Spirometric reference values for children living in Constantine (Eastern region of Algeria)

Mohamed Bougrida[1,2]; Mohamed-Kheireddine Bourahli[1,2]; Adel Aissaoui[1,2]; Sonia Rouatbi[3,4], Hacene Mehdioui[1,2], Helmi Ben Saad[3,4].

1. Service of Physiology and Functional Explorations. Ben Badis Hospital. Constantine. Algeria. 2. Laboratory of Research on Metabolic Diseases. Faculty of Medicine. Mentouri university. Constantine. Algeria. 3. Service of Physiology and Functional explorations. Farhat Hached Hospital. Sousse, Tunisia. 4. Laboratory of Physiology. Faculty of Medicine. Sousse. University of Sousse. Tunisia.

M. Bougrida, M.-K. Bourahli, A. Aissaoui, S. Rouatbi, H. Mehdioui, H. Ben Saad.

Valeurs de référence spirométriques des enfants de la ville de Constantine (Région de l'Est Algérian)

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RÉSUMÉ

Introduction : Élément clé de prise en charge pneumologique, la spirométrie oriente le diagnostic, offre une évaluation du handicap et permet un suivi évolutif des patients. Puisque la fonction respiratoire dépend essentiellement de la taille, de l'âge, du genre et du groupe ethnique, des équations de référence spirométriques, provenant d'individus sains, sont impératives pour l'interprétation des résultats.
But : Evaluer la nécessité de normes spirométriques pour les enfants âgés de 5 à 16 ans et vivants à Constantine (649 m d'altitude), une région de l'Est Algérien.
Méthodes: Les données anthropométriques et spirométriques sont mesurées chez 208 enfants Constantinois sains (101 filles).
Résultats : Les équations de référence publiées ne prédisent pas de façon fiable les données spirométriques mesurées chez les enfants constantinois. La combinaison du genre, de l'âge, de la taille, du poids, de l'indice de masse corporelle et de la surface corporelle, explique entre 69% et 94% de la variabilité des données spirométriques. Le rapport VEMS/CVF [moyenne±ET (5ème centile) de 0,91±0,06 (0,80) chez les garçons et de 0,90±0,06 (0,81) chez les filles] n'est pas inclus dans les équations de régression en raison d'absence de corrélation avec les données anthropométriques. La moyenne±ET du temps expiratoire est de 2,44±0,74 s et seulement 27% des enfants dépassent le seuil de 3 secondes. Dans un autre groupe prospectif de 24 enfants, la corrélation entre le VEMS mesuré et prédit par les nouvelles références locales est satisfaisante.
Conclusion : Nos équations de référence spirométriques propres aux enfants Constantinois, enrichissent la Banque mondiale d'équations de référence, à partir de laquelle les médecins peuvent choisir les normes en fonction de l'origine et de l'ethnie des patients.

Mots-clés

Pédiatrie, valeurs de référence; spirométrie; interprétation, Algérie

M. Bougrida, M.-K. Bourahli, A. Aissaoui, S. Rouatbi, H. Mehdioui, H. Ben Saad.

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SUMMARY

Background: Spirometry play an important role in diagnosing obstructive lung disease, assessing the severity of lung disease, monitoring treatment of patients with respiratory disorders, and allocating patients to treatment groups in drug intervention studies. Since spirometric lung function depends on body size, age, gender and ethnic group, reference equations derived from healthy individuals are imperative for interpreting results.
Aim : To assess the need for spirometric norms for children 5 to 16 years old and living in Constantine (Eastern region of Algeria).
Methods : Anthropometric and spirometric data were measured in 208 healthy children (101 girls) living in Constantine (649 m above sea level).
Results : Published reference equations did not reliably predict measured spirometric data in Constantinian children. Combination of gender, age, height, weight, body mass index and body surface area explained between 69% and 94% of the spirometric data variability's. FEV1/FVC ratio [means±SD (5th percentiles) were0.91±0.06 (0.80) for boys and 0.90±0.06 (0.81) for girls] was not included in the regression because of its relative independence of anthropometric data. The mean±SD of the forced expiratory time was 2.44±0.74 s and only 27% of children reached the threshold of ≥ 3 s. In an additional group of 24 children prospectively studied, the agreement between measured and predicted FEV1 was satisfactory.
Conclusion : Our reliable spirometric reference equations provide a useful norm for the care of paediatric patients living in the Eastern region of Algeria. The present study enriches the World Bank of reference equations, from which physicians should choose according to where patients live and their ethnic background.

Key-words

Pediatric ; Reference values ; Lung function ; Interpretation, Algeria

Spirometry play an important role in diagnosing obstructive lung disease, assessing the severity of lung disease, monitoring treatment of patients with respiratory disorders, and allocating patients to treatment groups in drug intervention studies [1-9]. Since spirometric lung function depends on body size, age, sex and ethnic group, reference equations derived from healthy individuals are imperative for interpreting results [1-5]. In routine testing, lung function is measured in members of given communities and then compared with predicted values derived from a 'relevant healthy' population with a different ethnic background or geographical location [7]. It's the case of Algerian pneumology departments where children measured spirometric values are compared with predicted values derived from other "healthy population" such as Iran [1], USA [2], China [3], England [4] or Tunisia [5] populations.
The need for local spirometric reference equations has been shown for Algerian adult population living in Constantine, an Eastern region of Algeria (ERA) [8]. For the Algerian children population; the applicability and reliability of the applied spirometric reference equations [1-5] should be assessed to avoid erroneous clinical interpretation and categorization in this population. Moreover, international guidelines recommend and encourage investigators to develop and publish specific spirometric reference equations for healthy individual, using the American thoracic society and the European respiratory society (ATS/ERS) guidelines [6].
Here we aim: 1) to test the applicability of some published spirometric reference equations [1-5] in healthy ERA children between 5 and 16 years old, and, if need be; 2) to establish spirometric reference equations for this population, and 3) prospectively assess their reliability.

DESIGN AND METHODS

Study design

Children were recruited over a 6-month period (September 2008, February 2009) from 6 schools in an ERA (Constantine area: 649 m above sea level). All children, Arabs aged from 5 to 16 years, were selected from several classes in each school. The spirometry manoeuvre was performed after the inclusion/non-inclusion criteria had been verified. Study approval was obtained from the ethics committee, and written informed consent was obtained from all children and their parents.

Sample size

For spirometry, a large number of subjects (i.e., n≥100) is needed to be confident that a significant difference between the published reference equations and the values from the local community does not exist [6]. Therefore, to establish reference equations, we recruited an initial group of 101 girls and 107 boys. To verify the reliability of our spirometric reference equations, we prospectively measured spirometric data in a second group of 24 additional healthy children (12 girls) who met the study inclusion criteria and had not participated in the first part.

Subjects

Prior to spirometric tests, each child was interviewed for a clinical assessment and detailed medical history. A standard Arab questionnaire, modified from that of Ferris [10], was used. School-doctor's reports were also used to find specific diagnosis. Only "healthy" non athlete's children, able to perform adequately spirometric tests, were included. A "healthy" children is defined as one in whom there is [11]: *i)* No presence of acute and no past chronic disease of the respiratory system; *ii)* No major respiratory disease, such as congenital anomalies, destructive type of pneumonia or thoracic surgery in past medical history; *iii)* No systemic disease which may directly or indirectly influence the respiratory system and general state of health (*e.g.* nasal, cardiovascular, neuromuscular, skeletal or renal disease); *iv)* No history of upper respiratory tract infection during 3 weeks prior to investigation; *v)* Normal body composition; *vi)* No more than incidental smoking experience; *vii)* Gestational age at least 37 weeks, and birth weight at least 2.5 kg; and *8)* No history of other than transient respiratory problems during the neonatal period. For children aged 5 years, another non inclusion criterion was a poor cooperation to achieve a standard spirometry, even after training with an incentive program [12].

Anthropometric measurements

The decimal age (accuracy to 0.1 years) was calculated from the date of measurement and the date of birth. Due to the failure of software to compute decimal age as the difference between test date and birth date, age was taken as the number of complete years from birth to the date of the study.
Standing height (cm) and weight (kg) were measured. Body mass index (BMI, $kg.m^{-2}$) and body surface area (BSA, m^2) [13] were calculated.

Spirometry function tests

Spirometry was carried out in the sitting position, and a nose clip was applied. To avoid the problem of variability due to different technicians and devices [14], all tests were performed, between 9.00 am and 1.00 pm, by one designated person at each school using one portable spirometer (ZAN 100, Me,greräte GmbH, Germany). The flow sensor of the spirometer, which was calibrated daily with a 3-liter syringe, is a hot-wire anemometer, and the range of air flow linearity is 0.01-16.00 l/s with an accuracy of ≥3% between 0.01 and 12.00 l/s. The following parameters were measured/calculated before and 15 minutes after inhalation of 400 μg of short acting $ß_2$-agonists (salbutamol): FVC (l); FEV_1 (l); forced expiratory flow when x% of FVC has been exhaled (FEF25%, FEF50% and FEF75%, $l.s^{-1}$), maximum mid expiratory flow (MMEF 25-75%), peak expiratory flow (PEF, $l.s^{-1}$), FEV_1/FVC ratio (absolute value) and forced expiratory time (FET, s).
Spirometry was performed according to the international recommendations [14]. The child was seated comfortably and he/she was instructed to take a full breath in, then to close the lips around the mouth piece and blow out as hard and fast as possible. Inspiration should be full and unhurried, and expiration tested should be continued without pause. In order to obtain maximal FVC, child was verbally encouraged to exhale as longer as possible. During the test, 3 to 4 children were watching the performance of their classmate, to reduce the need

for instructions before the start of the test. The FVC manoeuvre was considered well done if there was transient, maximal respiratory effort with no artefacts during the first second of the forced expiration, and if there was no premature termination (sharp decrease of expiratory flow). The objectives end of test criteria used to identify a reasonable FVC effort were [14]: *i)* The child cannot continue further exhalation. *Ii)* The volume–time curve shows no change in volume (<0.025 L) for ≥1 s, and the subject has tried to exhale for ≥3.

Spirometry data were expressed in "body temperature, barometric pressure and saturated". A minimum of three reproducible FVC measurements were obtained [14]. FVC and FEV_1 of the best 2 of the 3 selected measurements should not vary by more than 150 ml. The best FVC and the best FEV_1 were computed, even if the 2 values did not come from the same curve [14].

Data analysis

Preliminary descriptive analysis included frequencies for categorical variables and means±standard deviation (SD) for continuous ones.

Comparison with published reference equations

Measured FEV_1 was compared with predicted FEV_1 calculated from some published reference equations [1-5] for the same age range as in the corresponding study, in 2 ways. *i*. Individually measured FEV_1 were compared with the FEV_1 predicted [1-5] using paired *t*-tests and scatter plots. *ii*. As proposed by Bland and Altman [15] limits of agreement (LOA) were used for comparison, with individual difference (measured – predicted) plotted against the corresponding mean value. From these data, LOA were then calculated (mean difference between measured and predicted ±1.96 SD) [15]. The reference equation that provides the LOA closest to zero will be the most appropriate for our population [6].

Univariate analysis

The dependent spirometric data, expressed in logarithmic way, were normally distributed (except for $LogFEV_1/FVC$). T-tests and Pearson product-moment correlation coefficients I were used to evaluate associations between spirometric data and, respectively, gender and continuous measures.

Multiple regression analysis: spirometric reference equations

Various regression models were applied to the series to explain the spirometric reference equations, and the final selected one was the standard regression model as recommended [6, 11] and as selected by many others [3, 5]. This regression model includes the natural logarithmic values of both spirometric and anthropometric data. The other models tested included various transformations (linear, exponential, ...).

The choice of the appropriate regression model was made on the basis of 3 considerations: the highest explained variation of the dependent variable, the coefficient of determination (r^2), a constant residual standard deviation (RSD) and the lowest standard error (SE).

The 95% confidence interval was calculated [16]: 95% IC = 1.64≥RSD. A measured spirometric data lower than the lower limit of normal range (LLN = theoretical value – 95% IC) was considered abnormal.

Reliability of the spirometric reference equations

The reliability of our FEV_1 reference equations was evaluated in the second group of 24 healthy children. A Bland and Altman [15] technique compared the measured FEV_1, the predicted FEV_1 derived from our local equation and from the published equations [1-5].

Analyses were carried out using Statistica (Statistica Kernel version 6, StatSoft, France). Significance was set at the 0.05 level.

RESULTS

An initial sample of 252 voluntary children was examined. Non-inclusion criteria were found in 44 children.

Anthropometric and spirometric data

The number of children in each age group, the gender distribution and the anthropometric and spirometric data are given in table 1 and figure 1.

Forced expiratory time

The FET of the 208 children is shown in figure 1. In the total sample, significant positives correlations were found between FET and age, height, weight and BSA (respectively, r=0.75, r=0.78, r=0.80 and r=0.81).

The mean±SD (minimum-maximum) of the FET of the total sample children, of the children aged < 10 years (n=88) and of the children aged ≥ 10 years (n=120), were respectively, 2.44≥0.74 s (1.30-7.00), 1.98≥0.45 s (1.20-3.00) and 2.77≥0.73 s (1.50-7.00). Only 27%, 7% and 43% of children aged, respectively, 5-16 Yr, 5-10 Yr and 10-16 Yr, reached the recommended FET threshold of ≥3 s [14].

Comparison with published regression equations

Figure 2 (A-E) shows individually measured FEV_1 plotted against the corresponding predicted value for the same age range, using published reference equations [1-5].

Figure 3 shows the Bland and Altman [15] graphic representations, for the same age range, of comparisons between measured and predicted FEV_1 using published reference equations [1-5].

Except for the USA reference equations [2] (figures 2E and 3E), there was a systematic bias between the measured and predicted values for most of these equations [1, 3-5]. As can be seen (figure 2 A-D), the data showed narrow disparity compared with the identity line. This was particularly evident for the equations from China [3] (p=0.01) with wide LOA and systematic errors for the two sub-populations, girls and boys (figures 2A and 3A). The correlation between mean differences and mean values was also significant for the Iranian [1] (p=0.007) (figures 2C and 3C), Tunisian [5] (p=0.001) (figures 2D and 3D) and England [4] (p<0.001) (figures 2B and 3B) reference equations. Indeed, mean±SD measured FEV_1 was significantly overestimated by 0.27±1.65 l, 0.06±0.32 l and

Table 1 : Anthropometric and spirometric data in different age groups and in the total sample (n=208)

		Girls (n=26)	Boys (n=25)	Girls (n=32)	Boys (n=27)	Girls (n=21)	Boys (n=20)	Girls (n=23)	Boys (n=34)	Girls (n=101)	Boys (n=107)	Sample (n=208)
Anthropometric data												
Age	(Yr)	6±1	6±1	9±1†	9±1†	12±1†	12±1†	15±1†	15±1†	10±3	11±4	11±3
Weight	(kg)	21± 4	20±3	28±4†	30±7†	36±5†	35±6†	57±12†	55±9†	34±15	37±15	36±15
Height	(cm)	118±8	116±9	134±5†	135±71†	149±5†	147±8†	163±7†	166±8†	139±18	143±21	141±19
BMI	($kg.m^{-2}$)	15±2	15±1	15±1	17±3*†	16±1	16±1	21±4†	20±2†	17±3	17±3	17±3
BSA	(m^2)	0.83±0.10	0.81±0.09	1.03±0.09†	1.07±0.13†	1.24±0.09†	1.20±0.12†	1.60±0.18†	1.60±0.16†	1.15±0.30	1.20±0.33	1.18±0.32
Spirometric data												
FVC	(l)	1.38±0.30	1.32±0.26	1.96±0.25†	2.08±0.37†	2.48±0.39†	2.37±0.41†	3.38±0.54†	3.79±0.71*†	2.24±0.81	2.50±1.07*	2.37±0.96
FEV_1	(l)	1.30±0.29	1.21±0.28	1.76±0.22†	1.85±0.26†	2.33±0.38†	2.18±0.40†	3.11±0.45†	3.45±0.58*†	2.06±0.74	2.27±0.96	2.17±0.87
FEV_1/FVC	(absolute value)	0.92±0.05	0.90±0.07	0.90±0.05	0.89±0.06	0.93±0.06†	0.92±0.06	0.90±0.07	0.90±0.06	0.91±0.06	0.90±0.06	0.91±0.06
PEF	($l.s^{-1}$)	2.93±0.63	2.75±0.57	3.42±0.50†	3.64±0.61†	4.53±0.91†	4.46±0.67†	5.16±1.27	6.51±1.23*†	3.91±1.20	4.51±1.71*	4.22±1.51
FEF25%	($l.s^{-1}$)	1.10±0.26	1.00±0.22	1.34±0.26†	1.22±0.16*†	2.03±0.55†	1.71±0.49†	2.30±0.52	2.37±0.64†	1.64±0.62	1.63±0.71	1.63±0.67
FEF50%	($l.s^{-1}$)	2.04±0.40	1.91±0.39	2.46±0.29†	2.48±0.37†	3.48±0.74†	3.13±0.60†	4.12±0.97†	4.54±1.00†	2.93±1.02	3.13±1.25	3.03±1.14
FEF75%	($l.s^{-1}$)	2.72±0.54	2.55±0.48	3.14±0.39†	3.35±0.61†	4.26±0.92†	4.20±0.69†	4.94±1.27	6.04±1.19*†	3.66±1.19	4.18±1.61*	3.93±1.44
MMEF25-75%	($l.s^{-1}$)	1.90±0.41	1.75±0.54	2.26±0.3†	2.22±0.28†	3.19±0.65†	2.83± 0.65†	3.67±0.74†	4.01±0.89†	2.67±0.87	2.80±1.11	2.74±1.00
Expiratory time	(s)	1.72±0.37	1.83±0.41	2.22±0.34†	2.30±0.34†	2.42±0.38	2.30±0.37	3.31±0.57†	3.24±0.80†	2.38±0.70	2.49±0.77	2.44±0.74

0.06±0.33 l, respectively, with the Chinese [3], Iranian [1] and England [4] reference equations; and was significantly underestimated by 0.07±0.28 l with the Tunisian equations [5]. Using the USA equation [2], the difference with our measured FEV_1 was not significant (mean difference= -0.09±0.91 l; p=0.20) but with wide LOA (figure 3E).

Univariate analysis between anthropometric and spirometric data

In the total sample, gender significantly affected FVC, PEF and FEF75% (table 1). For the total sample, age, height, weight, BMI and BSA influence significantly all spirometric data, except for FEV_1/FVC (table 2).

Spirometric reference equations

Due to the inadequacy of the published (and locally applied) norms, we established reference equations adapted to our population, based on the multiple regression analysis.

For practical and routine interpretation of spirometric data, reference equations should include only easily measured or calculated anthropometric data, so we established simplified reference equations with six significant and independent predictors: gender, age, height, weight, BMI and BSA (table 2). Retained reference equations exposed in table 3, appeared to explain 69% till 94% of the spirometric data variability. We therefore used these models as the spirometric reference equations for our children population. After the predicted spirometric value for an individual child was computed from these equations, the LLN for the child could be obtained by subtracting 1.64Xrsd.

FEV_1/FVC ratio was not included in the regression because of its relative independence of anthropometric data (table 2). The mean±SD values for FEV_1/FVC were 0.91±0.06 for boys and 0.90±0.06 for girls (p>0.05), and the fifth percentiles were 0.80 and 0.81, respectively.

Reliability of the FEV_1 reference equation

Figure 4 shows individually prospectively measured FEV_1 plotted against the corresponding predicted value using published [1-5] (figure 4 A-E) and ERA (figure 4F) reference equations.

Figure 5 shows the Bland and Altman [15] graphic representations of the comparisons between measured and predicted FEV_1 using published [1-5] (figure 5 A-E) and ERA (figure 5F) reference equations.

The mean ± SD FEV_1 prospectively measured in the 24 children (11±3 Yr, 144±16 cm and 35±12 kg) was 2.27±0.76 l, representing 103±12% (range: 84 to 124%) of the predicted value calculated with our FEV_1 reference equations. The difference between the prospectively measured and predicted FEV_1 of these children was not significant (0.06±0.26 l, p=0.26) and the correlation was significant (figure 4F). The means±SD differences with our prospectively measured FEV_1 were not significant: 0.39±1.68 l, 0.02±0.43 l, 0.06±0.30 l, 0.09±0.31 l and 0.01±0.28 l, respectively, for the Chinese [3] (figures 4A and 5A), England [4] (figures 4B and 5B), Iranian [1] (figures

Table 2 : Spirometric reference equations for the Eastern region of Algeria

		Girls (n=101)					Boys (n=107)					Total sample (n=208)				
		Age	Height	Weight	BMI	BSA	Age	Height	Weight	BMI	BSA	Age	Height	Weight	BMI	BSA
FVC	(l)	0.90*	0.93*	0.91*	0.74*	0.95*	0.87*	0.93*	0.95*	0.76*	0.96*	0.88*	0.93*	0.93*	0.73*	0.95*
FEV_1	(l)	0.91*	0.94*	0.91*	0.72*	0.94*	0.89*	0.94*	0.95*	0.73*	0.96*	0.84*	0.94*	0.92*	0.71*	0.95*
FEV_1/FVC	(absolute value)	-0.01	-0.01	-0.08	-0.12	-0.06	0.10	0.06	-0.04	-0.18	-0.01	0.04	0.02	-0.06	-0.15	-0.03
PEF	($l.s^{-1}$)	0.76*	0.77*	0.73*	0.57*	0.77*	0.85*	0.89*	0.89*	0.69*	0.91*	0.80*	0.84*	0.81*	0.62*	0.84*
FEF25%	($l.s^{-1}$)	0.78*	0.79*	0.72*	0.55*	0.78*	0.76*	0.82*	0.81*	0.59*	0.83*	0.78*	0.81*	0.77*	0.56*	0.80*
FEF50%	($l.s^{-1}$)	0.82*	0.83*	0.81*	0.65*	0.84*	0.82*	0.86*	0.84*	0.62*	0.86*	0.82*	0.85*	0.83*	0.62*	0.86*
FEF75%	($l.s^{-1}$)	0.77*	0.76*	0.73*	0.58*	0.77*	0.85*	0.88*	0.89*	0.68*	0.90*	0.81*	0.83*	0.82*	0.62*	0.84*
MMEF25-75%	($l.s^{-1}$)	0.82*	0.82*	0.77*	0.58*	0.81*	0.80*	0.85*	0.83*	0.61*	0.85*	0.80*	0.84*	0.80*	0.59*	0.84*

For abbreviations, see list of abbreviations. * $p < 0,05$.

Table 3 : Univariate spearman's correlation coefficients (r) between the spirometric variables and anthropometric data

		Reference equations	r^2	SE	1.64 x RSD
FVC	**Girls (n=101)**	**Exp(-6.131+ 0.687 x LnBSA + 1.379 x LnH)**	**0.91**	**1.86**	**0.18**
(l)	**Boys (n=107)**	**Exp(1.583 + 1.934 x LnBSA – 0.296 x LnW)**	**0.94**	**0.76**	**0.18**
	TS (n=208)	Exp(2.585 + 2.338 x LnBSA - 0.602 x LnW)	0.92	0.53	0.18
FEV_1	**Girls (n=101)**	**Exp(-7.432 + 1.629 x LnH + 0.562 x LnBSA)**	**0.92**	**1.76**	**0.17**
(l)	**Boys (n=107)**	**Exp(2.984 + 2.603 x LnBSA – 0.750 x LnW)**	**0.94**	**0.73**	**0.17**
	TS (n=208)	Exp(-6.942 + 1.529 x LnH + 0.668 x LnBSA)	0.93	1.26	0.17
PEF	Girls (n=101)	Exp(-7.436 + 1.679 x LnH + 0.170 LnBMI)	0.64	0.71	0.29
($l.s^{-1}$)	Boys (n=107)	Exp(3.081 + 2.045 x LnBSA – 0.553 x LnW)	0.85	1.03	0.24
	TS (n=208)	**Exp(-8.947 + 1.967 x LnH + 0.073 x G + 0.203 x LnBMI)**	**0.77**	**0.42**	**0.27**
FEF25%	**Girls (n=101)**	**Exp(-8.749 + 1.750 x LnH + 0.240 x LnA)**	**0.69**	**2.10**	**0.34**
($l.s^{-1}$)	**Boys (n=107)**	**Exp(-11.297 + 2.233 x LnH + 0.230 x LnBMI)**	**0.76**	**0.66**	**0.33**
	TS (n=208)	Exp(-9.409 + 1.863 x LnH – 0.067x G + 0.189 x LnW)	0.73	1.22	0.33
FEF50%	**Girls (n=101)**	**Exp(0.392 + 0.804 x LnBSA + 0.240 x LnA)**	**0.77**	**0.26**	**0.26**
($l.s^{-1}$)	**Boys (n=107)**	**Exp(-9.040 + 1.929 x LnH + 0.159 x LnW)**	**0.82**	**1.37**	**0.27**
	TS (n=208)	Exp(-10.098 + 2.132 x LnH + 0.217 x LnBMI)	0.80	0.41	0.26
FEF75%	Girls (n=101)	Exp(0.516 + 0.544 x LnBSA + 0.298 x LnA)	0.63	0.30	0.30
($l.s^{-1}$)	Boys (n=107)	Exp(3.359 + 2.205 x LnBSA -0.661 x LnW)	0.84	1.06	0.25
	TS (n=208)	**Exp(-9.067 + 1.968 x LnH + 0.065 x G + 0.219 x LnBMI)**	**0.75**	**0.44**	**0.28**
FEF25-75%	**Girls (n=101)**	**Exp(-4.312 + 0.818 x LnH + 0.328 x LnA + 0.136 x LnW)**	**0.71**	**2.14**	**0.28**
($l.s^{-1}$)	**Boys (n=107)**	**Exp(-10.561 + 2.242 x LnH + 0.148 x LnBMI)**	**0.78**	**0.60**	**0.30**
	TS (n=208)	Exp(-9.911 + 2.122 x LnH + 0.132 x LnBMI)	0.75	0.46	0.29

TS: Total sample. BSA: body surface area (m^2). H: height (cm). W: Weight (kg). BMI: body mass index (kg/m^{-2}). G: Gender [0. Girls. 1. Boys). Exp: exponential. Ln: natural logarithm. For the other abbreviations, see list of abbreviations. Retained reference equations are in fatty characters.

4C and 5C), Tunisian [5] (figures 4D and 5D) and USA [2] (figures 4E and 5E) reference equations. LOAs were wide using some reference equations [1, 3-5] and narrow using the USA reference equation [2].

DISCUSSION

Published and locally applied spirometric reference equations, except for the USA norms, did not reliably predict measured FEV_1 data in Constantinian children. Thus, by using gender and anthropometric data as independent predictors, we established natural logarithmic spirometric reference equations that explained between 69% and 94% of the parameters variability's. In an additional group of healthy children prospectively assessed, our FEV_1 reference equations yielded satisfactory predictions.

Study design

In a recent study [17] aiming to establish the number of local subjects required to validate published reference values, it was found that at least 150 males and 150 females would be necessary to validate reference values to avoid spurious differences due to sampling error. Our study sample size (n=208) was higher than in other studies [Kaditis et al. [18] (n=152), Pesant et al. [19] (n=164)], was closer to that of other recent studies [Brouwer et al. [20] (n=204); Jeng et al. [21] (n=214), Vilozni et al. [22] (n= 242); Tsai et al. [23] (n=309)], but was smaller than in previous studies (table 4). However, our reference equations explained between 69% and 94% of the data variability's, which appears to be satisfactory.
Although no statistical methods were used to choose the children, the number studied and the fact that many schools in different areas of Constantine were included give a reasonable degree of confidence in the data.

Table 4 : FEV1, FVC and FEV1/FVC ratio published reference equations

Country [reference]	Age range (Yr)	Gender (n)	Parameters	Equations	r^2	Interpretation
China [3]	7-19	Girls (n=460)	FVC	Exp(-13.270 + 2.835 x LnH)	0.79	LLN= 0.19
			FEV_1	Exp(-13.392 + 2.972 x LnH)	0.90	LLN=0.17
			FEV_1/FVC	Not done	?	?
		Boys (n=392)	FVC	Exp(-13.851 + 2.964 x LnH)	0.90	LLN=0.17
			FEV_1	Exp(-13.999 + 2.843 x LnH)	0.79	LLN=0.18
			FEV_1/FVC	Not done	?	?
Tunisia [5]	6-16	Girls (n=533)	FVC	Exp(-12.4071 + 2.6706 x LnH)	0.89	LLN=0.21
			FEV_1	Exp(-12.1922 + 2.6035 x LnH)	0.88	LLN=0.21
			FEV_1/FVC	Exp(4.8786 - 0.0788 x LnH)	0.04	LLN=0.28
		Boys (n=581)	FVC	Exp(-13.0169 + 2.8008 x LnH)	0.90	LLN=0.21
			FEV_1	Exp(-12.7686 + 2.7243 x LnH)	0.90	LLN=0.21
			FEV_1/FVC	Exp(5.0419 - 0.1155 x LnH)	0.05	LLN=0.36
USA [2]	8-18	Girls (n=456)	FVC	-1.2082 + 0.05916 x A + 0.00014815 x H^2	0.87	LLN: -1.2082 + 0.05916 x A + 0.00012198 x H^2
			FEV_1	-0.8710 + 0.06537 x A + 0.00011496 x H^2	0.85	LLN: -0.8710 + 0.06537 x A + 0.00009283 x H^2
			FEV_1/FVC	90.809 - 0.2125 x A	0.39	LLN: 81.015 - 0.2125 x A
		Boys (n=422)	FVC	-0.2584 - 0.20415 x A + 0.010133 x A^2 + 0.00018642 x H^2	0.87	LLN: -0.2584-0.20415 x A + 0.010133 x A^2 + 0.00015695 x H^2
			FEV_1	-0.7453-0.04106xA+0.004477xA^2+0.00014098xH^2	0.85	LLN: -0.7453-0.04106xA+0.004477xA^2+0.00011607xH^2
			FEV_1/FVC	88.066-0.2066 x A	0.34	LLN: 78.388 - 0.2066 x A
Iran [1]	5-20	Girls (n=310)	FVC	0.03510 x H +0.06651 x A - 3.2230	0.86	LLN: 0.0310 x H + 0.06651 x A - 3.2230
			FEV_1	0.02959 x H + 0.06588 x A - 2.732	0.87	LLN: 0.0260 x H + 0.06588 x A - 2.732
			FEV_1/FVC	-0.0313 x H + 0.184 x A + 90.624	0.02	LLN: -0.069 x H + 0.184 x A + 90.624
		Boys (n=491)	FVC	0.04202 x H + 0.09678 x A - 4.322	0.90	LLN: 0.0370 x H + 0.09678 x A - 4.322
			FEV_1	0.03569 x H + 0.09030 x A - 3.683	0.90	LLN: 0.0310 x H + 0.09030 x A - 3.683
			FEV_1/FVC	0.011935 x H - 0.13572 x A + 88.2983	0.02	LLN: 0.0101108 x H - 0.13572 x A + 88.2983
England [4]	4-19	Girls (n=317)	FVC	< 152.6 cm: 0.039 x H - 3.311 > 152.5 cm: 0.045 x H - 3.881	?	?
			FEV_1	< 152.6 cm: 0.033 x H - 2.734 > 152.5 cm: 0.041 x H - 3.680	?	?
			FEV_1/FVC	100 x (-0.00098 x H + 1.04)	?	?
		Boys (n=455)	FVC	< 162.6 cm: 0.043 x H - 3.619 > 162.5 cm: 0.068 x H - 7.038	?	?
			FEV_1	< 162.6 cm: 0.034 x H - 2.780 > 162.5 cm: 0.052 x H - 5.108	?	?
			FEV_1/FVC	100 x (-0.001 x H + 1.00)	?	?

FEV_1: 1's forced expiratory volume (l). FVC: forced vital capacity (l). n: number. Exp: exponential. Ln: natural logarithm. H: height (cm). W: weight (kg). r^2: coefficient of determination. LLN: lower limit of normal range.

For daily clinical practice, the 8 recommendations applied as inclusion criteria [11] seem to be feasible and practicable. Therefore, the present study produces useful results for the interpretation of spirometric children data with chronic disease living in this area, provided that the factor of altitude is taken into account, Constantine being 649 m above sea level.

Spirometric procedure and statistical methods

We have applied the recent recommendations [6] to compare used reference equations [1-5] in Algerian lung exploration departments with measurements performed on our representative sample of healthy children.

ERA reference equations, that provide the sum of residuals (log observed – log predicted for each child) closest to zero, were considered to be the most appropriate for our population [6, 11]. As recommended [6], we have included explicit definitions of the LLN ranges. As our natural logarithmic reference data have a normal distribution, the lower 5th percentiles have been estimated as the 95% CI using Gaussian statistics.

Limits of the present study

In addition to the anthropometric data, many other factors should be taken account.

Nevertheless, the relationships between children spirometric data and some specific data [7, 24-26] (birth weight or height, lean body mass, nutritional status, waist size, living environment, physical activity level's, socioeconomic levels, puberty, parental smoking, altitude), should be evaluated.

Spirometric data predictors

Similar to previous reports [1-5, 27], measured spirometric data (table 2) increased with increasing age, height and weight with the best correlation being to height. The fact that anthropometric data affect the results of lung function tests in children has been shown repeatedly in previous reports [1-5]: age, height, and weight play high parts in modulating the results of spirometric tests; this makes sense because these three indices go hand in hand in children (figure 1).

We found that BMI and BSA were also significant predictors that influence the spirometric data, with a high correlation (better than this with height) for BSA (table 2). These two predictors haven't been previously evaluated in the five spirometric reference equations applied actually in Algeria [1-5]. Unlike in some healthy children studies [1-5], where weight has no significant effect on spirometric data (table 4), our study (tables II and III), supported by data from other workers [28-31], show that weight and BMI seems to play an additional part in influencing the results of the spirometric tests. However, the correlation between spirometric data and BSA was previously evaluated: while some authors found no correlation [32], others have demonstrated a significant positive correlation with PEF rate (r=0.64 [31]). Only few authors had included BSA as an independent predictor in spirometric reference equations [32]. Our result could be interesting since BSA was found to be the best general predictor of the children ventilatory variable in normal children during rest and exercise [32].

Forced expiratory time

The ATS/ERS [6] recommend as an end of test criteria that the child has tried to exhale for ≥3 s in children aged <10 yrs and for ≥6 s in subjects aged ≥10 yrs. In a retrospective study done on 117 children aged 4-10 years, Tomalak et al. [33] found *(i)* closer values to theses observed in the present study (FET means≥SD of 2.2±1.2 s vs. 1.98≥0.45 s, respectively) but with wide ranges [minimum-maximum: 0.71-6.9 s vs. 1.20-3.00, respectively); *(ii)* Higher percentage of children reaching the FET threshold of ≥3 s (24% vs. 7%, respectively); and *(iii)* as in the present study, they found a significant correlation between FET and the age of the children 5-10 years (respectively, r=0.59 and r=0.35).

A FET ≥3 s was achieved by only 27% children; however, FET significantly correlated with age (r=0.75), which may explain such a low percentage. Similar observations were made by other authors [34, 35]. It seems that the actual standards are too restrictive and specific recommendations regarding the FET for children should be developed [33].

Choice of the appropriate reference equations

We found significant differences between measured and predicted FEV_1 from the published, and locally used, reference equations [1-5] (figures 2-3). The implications of this for children with pulmonary chronic disease may be considerable and include potential errors regarding, diagnosis and classification of impairment, and unrealistic expectations for therapeutic interventions designed to improve pulmonary capacity [36]. This argues for the use of specific reference equations and confirms the international recommendation to continue establishing regional equations [6,13].

For purely practical reasons, we established spirometric reference equations that included BSA, height, weight, BMI and age as independent variables: r^2 values in the present FEV_1 and FVC reference equations are similar or even higher than whatever other groups have presented [1-5] (table 5).

Figures 3 and 4 provide strong arguments for the use of our specific reference equations with very satisfactory reliability. They illustrate the errors that may arise from using other FEV_1 reference equations [1-5] in this population. Therefore, given its high reliability, we propose that our spirometric reference equations be used in Constantinian and ERA children.

ERA spirometric reference equations

After accounting for height in the regression analysis, the contribution of other parameters (age, weight, BSA and BMI) was important, justifying their use in the final derivation of the reference equations (table 3). Logarithmic transformation of lung function parameters and anthropometric data, which has been used by previous investigators [3,5] was necessary to achieve normal distributions and to stabilize the variance. It may be argued that the use of logarithms makes the reference equations difficult to apply in medical practice.

In contrast to some studies [1-5, 28] (table 4), and similar to others [37, 38], the values of FEV_1/FVC in the present study healthy children's were independent of anthropometric data (table 2) and therefore no prediction equations were derived. The reported means and 5th percentile values for FEV_1/FVC can be used as reference normal values in our population.

Among the numerous studies reporting spirometric prediction equations in children and adolescents in different areas of the world, there are only six published studies from Arab countries [5, 28, 31, 37, 39, 40]: some are relatively old and yet none provided prospective verification in their populations. So, the present study enriches the World Bank of reference equations, from which physicians should choose according to where patients live and their ethnic background.

Spirometric data interpretation

Two approaches to interpreting children spirometric data have been proposed [6, 11]: either by calculating the LLN or by fixing a percentage (80% of predicted value) below which the spirometric value is considered abnormal. With the LLN approach, which appears to be the appropriate method [1, 3-5], no child prospectively evaluated was below the normal range. The practice of using 80% predicted as a fixed value for the LLN may be acceptable in children [6]: using the 80% fixed percentage in our sample, no child prospectively evaluated had "abnormally low" FEV_1 or FVC.

When using a set of reference equations, extrapolation beyond the size and age of investigated subjects should be avoided [6, 11]. As with all predictive equations, they are only valid for this specific group, i.e. children aged 5-16 years, with a height of 95-181 cm (boys) and 100-177 cm (girls) and with a weight of 17-75 kg (boys) and 13-85 kg (girls). If a patient's data are outside the limits of ERA reference population, a statement in the interpretation should indicate that an extrapolation has been made.

Perspectives

The criteria for disease severity established by international guidelines [6, 9] are based on FEV_1 expressed as a percentage of the predicted value after application of a bronchodilator. So it is interesting, as done in adults [41, 42], to determine ERA post-bronchodilator spirometry reference values. Also, in order to diagnosis restrictive defects, it's interesting to establish, as done in North African adults populations [8,43], lung volumes in healthy children.

In conclusion, we established reliable reference equations to interpret the results of spirometry in healthy ERA children. Using these reference equations, spirometric data can be easily predicted from simple parameters of age, height, weight, BMI and BSA, and obstacles to interpretation are avoided.

Figure 1 : The forced expiratory time (s) in subgroups of children, according to age (figure 1A), height (figure 1B), weight (figure 1C), and body surface area (BSA) (figure 1D) ranges.
n = number of children.
Data are shown as box-and-whiskers-plots illustrating the mean (?), standard deviation (I).
• $p < 0.05$: Comparison (Test Student) from one range to the next.
• NS: not significant.

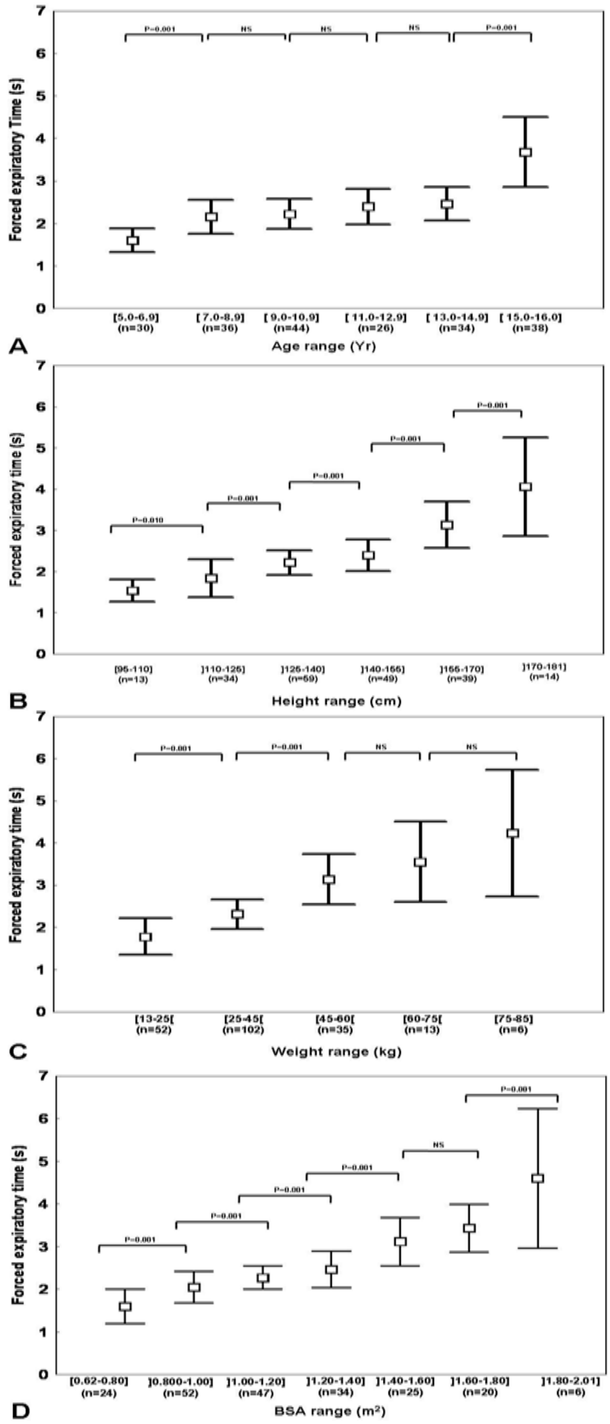


Figure 2 : Comparison with published spirometric reference equations. Comparison, for the same age range, of measured and predicted 1's forced expiratory volume (FEV1) determined from China [3] (figure 2A), England [4] (figure 2B), Iran [1] (figure 2C), Tunisia [5] (figure 2D) and USA [2] (figure 2E) reference equations.
n = number of subjects having the age range of the predicted FEV1 study. r: correlation coefficient. p: probability.
: line of identity
------- : linear regression line.

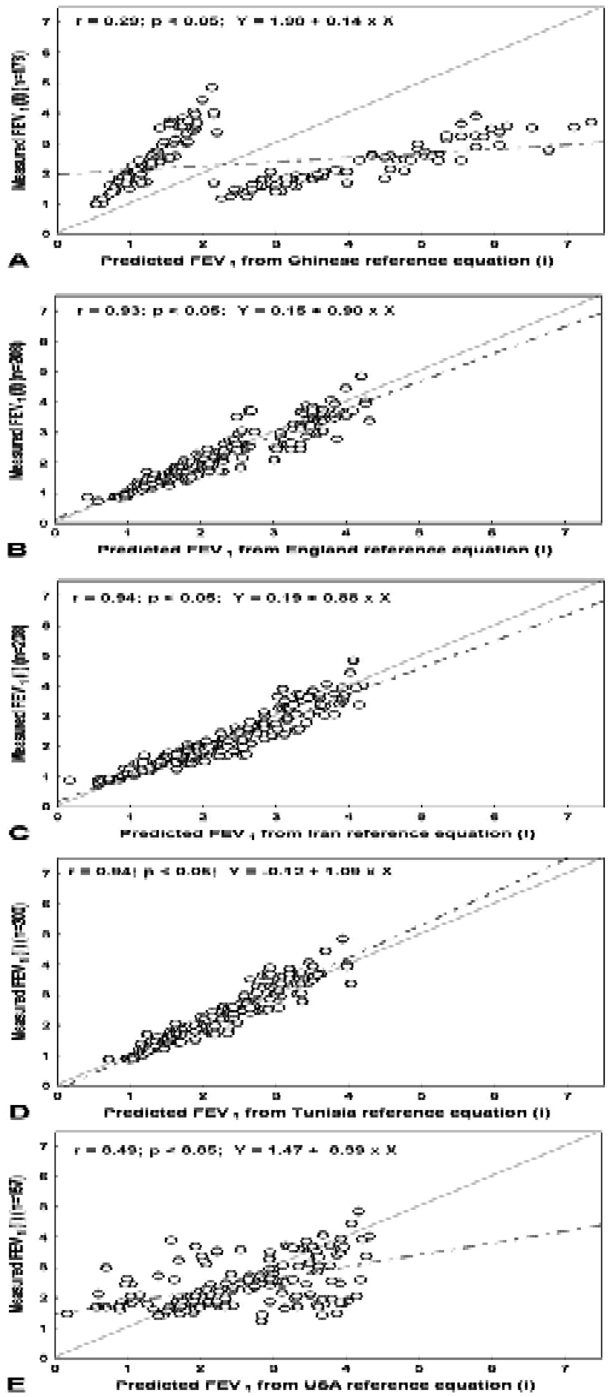


Figure 3 : Bland and Altman representation between measured and predicted 1's forced expiratory volume (FEV1) determined from China [3] (figure 3A), England [4] (figure 3B), Iran [1] (figure 3C), Tunisia [5] (figure 3D) and USA [2] (figure 3E) reference equations.
n: number of subjects having the age range of the predicted FEV1 study.
- - - - - : linear regression line.
: Mean ±1.96 standard deviation.

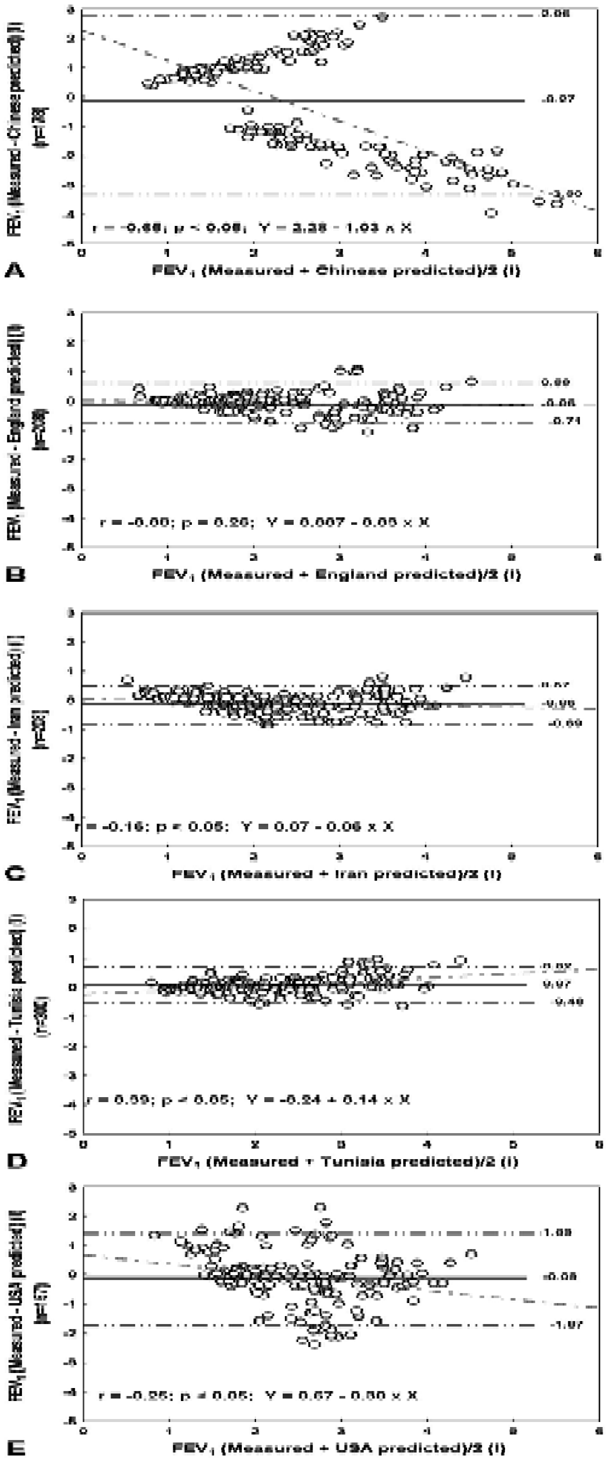


Figure 4 : Comparison of prospectively data (n=24 children) with published spirometric reference equations.
Comparison of measured and predicted 1's forced expiratory volume (FEV1) determined from China [3] (figure 4A), England [4] (figure 4B), Iran [1] (figure 4C), Tunisia [5] (figure 4D), USA [2] (figure 4E) and ERA (figure 4F) reference equations.
n = number of subjects. r: correlation coefficient. p: probability.
: line of identity
------- : linear regression line.

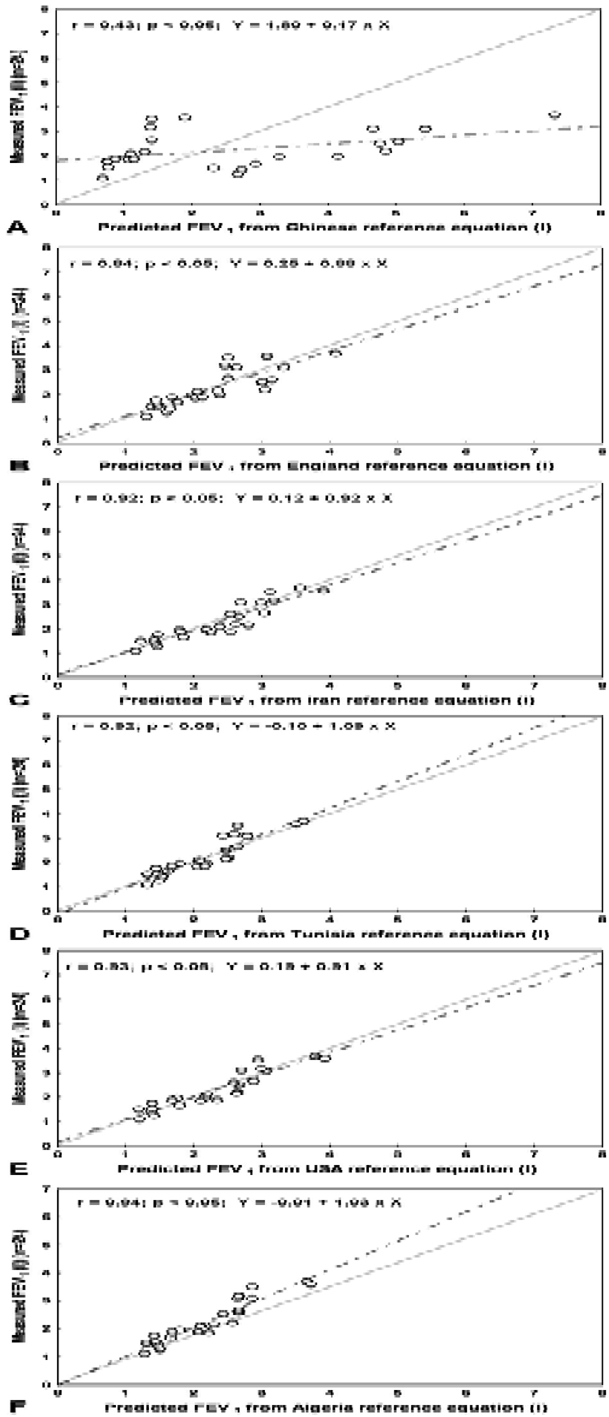
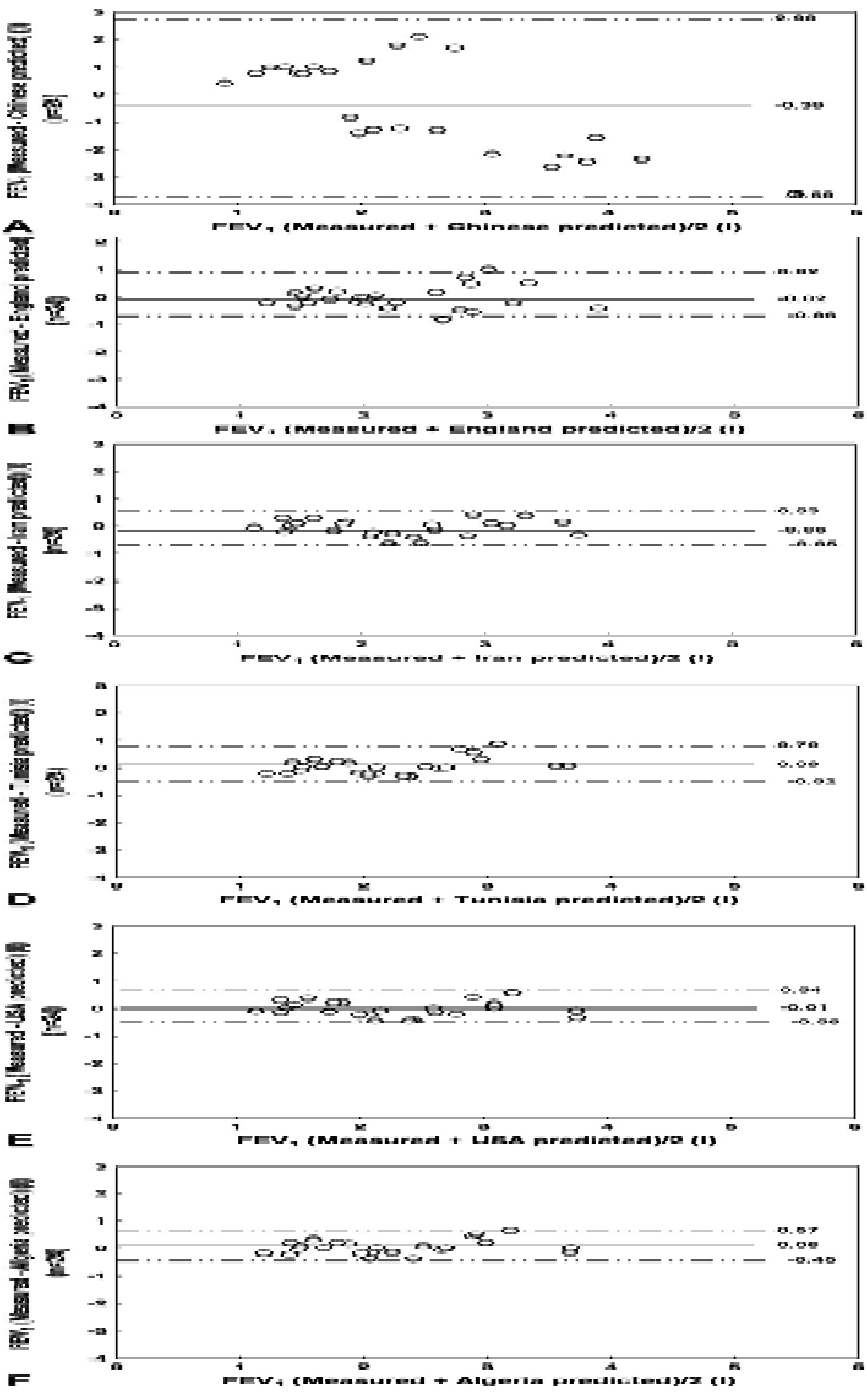


Figure 5 : Bland and Altman representation between prospectively measured and predicted 1's forced expiratory volume (FEV1) in 24 children, determined from China [3] (figure 5A), England [4] (figure 5B), Iran [1] (figure 5C), Tunisia [5] (figure 5D), USA [2] (figure 5E) and ERA (figure 5F) reference equations.
n: number of subjects.
- - - - - : linear regression line.
: Mean ±1.96 standard deviation.



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