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Rim Dridi, Nadia Dridi, Amira Zouita Ben Moussa, Paulo T. Muller, Zouhair Tabka, et al.. Pulmonary diffusing capacity measured by NO/CO transfer in Tunisian boys. Pediatric Pulmonology, 2020, 55 (10), pp.2754-2761. 10.1002/ppul.24984 . hal-02929390v2

HAL Id: hal-02929390

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Pulmonary diffusing capacity measured by NO/CO transfer in Tunisian boys

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Running head: Pulmonary Diffusing capacity in Tunisian youth.

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Abbreviations

BSA: body surface area

CO: carbon monoxide

Dm: membrane component of alveolar -capillary transfer of gases ($mL.min^{-i}.mmHg^{-1}$)

Dm_{Co}: membrane component of alveolar -capillary transfer of carbon monoxide ($mL.min^{-i}.mmHg^{-1}$)

Dm_{NO}: membrane component of alveolar -capillary transfer of nitric oxide ($mL.min^{-i}.mmHg^{-1}$)

H: height (cm)

He: helium

TL_{CO}: pulmonary diffusing capacity for carbon monoxide ($mL.min^{-i}.mmHg^{-1}$)

TL_{NO}: pulmonary diffusing capacity for nitric oxide ($mL.min^{i}.mmHg^{1}$)

kg : kilograms

ms : millisecond

NO : nitric monoxide

N_2: nitric dioxide

PO_2: oxygen partial pressure (mmHg)

VA : alveolar volume (L)

Vc : capillary blood volume (mL)

W: weight (kg)

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Abstract

Background: The diffusing capacity, which measures gas-exchange, uses reference values based on data from American or European studies. There are currently no reference values of pulmonary diffusing capacity (TL) and its components such as the conductance of the membrane (Dm) and capillary lung volume (Vc) for healthy North African children**.**

Objectives: We determined the prediction equations - reference values for TL, Dm, Vc and the alveolar volume (VA) in healthy Tunisian boys.

Methods: Values of Vc, Dm, TL and VA were measured by the NO/CO transfer method, using a single breath manoeuvre in 118 Tunisian boys (8 to 14 years old) at rest. We performed linear regression analysis of the pulmonary parameters and independent variables such as height, weight and age.

Results: The reference equations for TL_{CO} was 0.201 * weight (kg)+8.979; for TL_{NO} was 0.76*height (cm)-24.383; for Dm was 0.388* height (cm)- 12.555 and for VA was 0.34*height (cm)-3.951. Vc increased significantly with weight ($p<0.05$) but not with age ($p>0.05$).

Conclusions: References norms for TL_{CO} and TL_{NO} and its components in young Tunisian boys are similar to data from other countries. The prediction equations we developed can be extended to clinical practice in Tunisia and can be considered for use in neighboring North African countries.

Key words: membrane diffusing capacity - capillary lung volume – respiration - North Africa.

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Introduction

Reference values of pulmonary function in children are needed for both physiological and clinical measurements of pulmonary diffusing capacity (TL) when assessing gas exchange [1, 2]. Abnormalities in TL can reflect pathological changes in the lung, making pulmonary diffusing capacity important in the assessment of lung function [1,3]. Several studies are based on data from North American, Asiatic or European children, with no reference values of pulmonary diffusing capacity and its components (i.e., the diffusing capacity of the membrane (Dm) and the capillary lung volume (Vc) that can be applied to healthy north-African children. Asiatic references have been compared with Caucasians either European [1] or North American children [3]. Indeed, studies by Kim et al. (2016) reported that African-American have lower DLCO and VA compared to Caucasians children for the same height, gender, and age, while Katidis et al, (2008) suggested that genetic characteristics of Greek Roma children may not be similar to those of Roma subjects living in other European countries and in America. Moreover, it is generally accepted that Caucasians children have higher spirometric values than children from other ethnic groups (Alexandraki et al. 2010). It is likely that children from other ethnic backgrounds (e.g. Northern and Southern European) could have different anthropometric features, leading to limitations of many reference equations. Moreover, equations from Caucasian groups may not be suitable for use in other ethnic populations [4] and it is important to continue to develop normative data for children of differing ethnicities [3]. Thus, it is important to study the spirometric parameters and their correlations with the physical characteristics in North African children.

Current reference equations might be inappropriate for use in children for several reasons. First, reference data were mostly collected decades ago, and could be outdated because the physical characteristics of the paediatric population has changed due to improved health and nutrition [5]. Furthermore, temporal changes in growth and maturation (secular trend) can

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influence lung volumes and diffusion capacity [6,7]. Moreover, measurement protocols and analytical techniques have improved in recent years. Second, age was rarely considered as a determinant of pulmonary function, including when establishing reference equations [8, 9]. Third, reference values for lung volumes and diffusion capacity were often derived from studies with relatively small population sizes [10].

Studies on reference values for non-Caucasians are needed [4, 11] because the usefulness of values obtained in Caucasian children is limited by ethnic differences in pulmonary function [3, 4, 12-15]. Other studies reported lung volumes in Gypsy children [16], Greek infants and adolescents [17] and Chinese descent [18, 19], but these equations may not be suitable for use in other ethnic populations, making it important to develop reference data for children of differing races and ethnicities. In addition, there is a lack of spirometric data on North African children mainly due to the absence of equipment in this region [20]. To the best of our knowledge, there are no studies reporting values of pulmonary diffusing capacity and its components in Tunisian boys.

The objective of our study was to develop prediction equations for pulmonary diffusing capacity for carbon monoxide (TL_{CO}) and pulmonary diffusing capacity for nitric oxide (TL_{NO}) based on anthropometric data (height and weight) of Tunisian boys (8-14 year).

Predicted equations are useful as they may improve accuracy and reduce variability in assessments. Such information may be of particular importance when providing care to Tunisians boys and also more generally to public health services in North-African countries.

Materials and methods

Study population

The University Ethics Committee (University of Sousse, Tunisia) approved the experimental protocol in accordance with the Declaration of Helsinki. Written informed consent was obtained from each child and from their parents prior to enrolment in the study. Children were selected from the city or the suburbs of Sousse in Tunisia, which is a lightly industrialized area and has low levels of air pollution. The experiment was conducted over a 3 months period (from December, 2018 to February, 2019).

The children or their parents were asked to complete a health questionnaire prior to participation in the study. The questionnaire was related to age, previous or current pulmonary diseases, allergies, other diseases, and current and previous medications. Tunisian boys (n=118) aged 8 to 14 years were enrolled for this study. Puberty was not taken into account as a predictor of diffusing pulmonary capacity in this study since all pubescent children were removed and only pre-pubescent children were studied.

Children who used bronchodilators were excluded from the study, as were children who were unable to co-operate or perform adequate respiratory manoeuvres. Each participant had great-grandparents, grandparents and parents who were of Tunisian descent.

Clinical evaluation

Information regarding prior and current health status was obtained from a questionnaire so that could obtain a socio-economically homogeneous population [21]. All participants underwent a physical examination and findings or signs of puberty (breast development, pubic hair) were noted. All participants were non-smokers, with normal lung volumes and flow-volume curves at rest and with no history of cardiopulmonary diseases or allergies (Table 1).
Height and weight were collected without shoes to the nearest 0.1 cm and 100 grams respectively, using standard stadiometers (Seca™, Hamburg. Germany) and scales (Tefal, France). Age was calculated by the difference between the date of birth and participation date and was recorded.

TL_{CO} and TL_{NO} Measurements

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Values for lung capillary blood volume (Vc), membrane diffusing capacity (Dm), lung transfer (TL) and lung volume (VA) were measured by the NO/CO transfer method to determine lung diffusing capacity.

Each participant performed two validated transfer measurements under resting conditions. The validity of the transfer measurement was confirmed by ensuring that each child performed the manoeuvre without hesitation with his mouth tightly closed around the mouth-piece and was able to hold his breath for the duration of the measurement.

The procedure was validated by examining the output of lung volume displayed on the screen during the manoeuvre; the trace should have no pauses during the fast inspiration, when holding the breath hold and during expiration. We used the average of two values that differed by less than 10% from each other. All children were previously trained in the requirements for the measurements, and additional measurements were made as required.

Measurements of TL_{NO} and TL_{CO} were made simultaneously during a single breath manoeuvre [8] using an automated apparatus (Medisoft Dinant™, Belgium). The inhaled gas mixture contained 0.28% CO, 14% He, 21% O_2 balanced with N_2 and 450 ppm NO in N_2 (Air Liquide Santé. Tunisia), resulting in a final concentration of 40 ppm NO in the inspiration bag. The apparatus was calibrated daily with the gas mixtures using automated procedures. Linearity of the analysers were factory checked, and the pneumotachograph (PTG) was calibrated with a 2L syringe.

The participants breathed through a mouthpiece containing a filter that was connected to the PTG. The child was requested to make a deep expiration, and a valve then allowed the child to inspire the air mixture during a rapid deep inspiration. A forced apnoea period of 4 seconds was then followed by a deep expiration. The first 0.6L of the expired gas was rejected and the next 0.6L was automatically analysed for carbon monoxide (CO), nitric oxide (NO) and

Accepted manuscript

helium (He) with a delay of 35s. The lung volume during the apnoea was calculated using the He dilution technique.

The reproducibility of the method was previously tested in 10 children who performed six consecutive trials on different days. Diffusing capacity of alveolar membrane (Dm_{CO}) and lung capillary blood volume (Vc) values were derived from TL_{NO} and TL_{CO} values as previously described [20, 22]. In brief, a rapid reactivity of NO and haemoglobin was assumed (and the reverse negligible**)**, so that the TL_{NO} value was considered to be equivalent to Dm_{NO}. The value of Dm_{CO} was calculated by assuming proportionality of the two gases to be 1.97. The reactivity of CO with haemoglobin at a PO_2 of 110 mmHg was derived from published measurements made at physiological pH [22, 23].

Data Analysis

Subject characteristics are expressed as mean and standard deviation (±SD). Normal distribution of the data was tested using the Kolmogorov-Smirnov test. Single and multiple linear regressions of the dependent variables (TL, Dm and Vc) and independent variables (height, weight, age) were performed. A value of $p<0.05$ was considered significant. Statistical analysis was performed using regression analysis with the STATVIEW (version13) software.

Results

The demographic and measured outcomes from the 118 Tunisian boys participating in the study (8 years old, n=2; 9 years old, n=11; 10 years old, n =16; 11 years old, n=44; 12 years old, n=32; 13 years old, n=3 and 14 years old, n=10) are summarized in ***Table 1.***

Accepted manuscript

Pulmonary diffusing capacity and its components (the diffusing capacity of the membrane (D(m)), capillary lung volume (V(c)) and VA) were all related to age, weight and height. The regression analysis of TLco, VA and Vc plotted against weight and are shown in ***Figure 1.*** Height was a predictor of alveolar volume (VA), carbon monoxide diffusing capacity (TL_{CO}), and capillary volume (Vc) as shown in ***Figure 2.***

The regression coefficients using height and weight as the independent variables are summarized in ***Table 2***. Values for Dm and TL_{NO} were dependent on height and not on weight, while values for TL_{CO} and V_C were dependant on weight only and alveolar volume (VA) correlated with both height and weight ***(Table 2)***.

The measurements from the study also provides prediction equations for the relationship between pulmonary diffusing capacity (TL) and its components (the conductance of the membrane (D(m)), capillary lung volume (V(c)) and body surface area (BSA)) in healthy children. Moderate positive correlations were found between the diffusion parameters: Dm ($r=0.39$; $p= 0.001$), TL_{NO} ($r=0.39$; $p= 0.001$), TL_{CO} ($r=0.46$; $p= 0.000$) and Vc ($r=0.4$; $p= 0.001$). However, BSA best correlated with TL_{CO} ($r=0.46$) ***(Figure 3C)*** and to a lesser degree with Dm ($r = 0.38$; $p=0.001$) ***(Figure 3D).***

Discussion

This study provides predictive equations of pulmonary diffusing capacity components measured by the NO/CO transfer method in healthy young Tunisian boys. Our results confirm previous observations [1, 16] that height and body weight are key individual predictors of TL_{NO} and TL_{CO}, and that alveolar volume (VA) was related with both height and weight.

Predictive equations are generally valid for the specific group from which they are generated, which in our study is based on Tunisian boys aged 8-14 years, with weights of 25-64kg and heights of 126-170cm. Including age in the regression analysis did not affect the relationship

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with the other dependent variables, although there were increases in TL_{CO} and Vc with greater weight. The increased in lung function in this period of growth in children could be explained by changes in lung volume and muscle strength [20, 24-26]. For example, maximum muscle strength can explain the apparent acceleration in male lung function with increasing height [24]. Our suggestion that height is the most important variable in the equations predicting pulmonary diffusing capacity and its components values is in agreement with other studies [25]. Body growth probably affects pulmonary function parameters [1, 19] and height is a dependant variable in spirometric factors [3,4, 27,28], although there are large variations due to ethnic influences and socio-economic factors [3,16,29]. Thus, pulmonary diffusing capacity values from Tunisia with data from British [1], Mediterranean [30] or Caucasian USA [31] cohorts yield differences in lung function.

Values of Dm in our study are higher than those of most European studies, while values of Vc are lower than values from studies in the USA [31]. However, we found differences in pulmonary diffusing capacity for carbon monoxid (TLCO) and alveolar volume (VA) between our results and data reported by previous studies, using other equipment, methods and analytical techniques. (Table 3). But our values for TL_{CO} and VA are very similar to those reported for African-American children [3] of comparable size

These differences could be related to variations in methodology, sampling variability, patient characteristics and variations in body morphology and lung function in different ethnicities [14,32]. For example, eleven-year-old Negro boys [33], pre-pubertal North American children [34] or young Turkish boys [35] had values for Vc similar to those reported in our study.

Our values for TL_{NO} /VA are lower than those predicted by Stam and al [36]. However, our study indicates moderately positive correlations between BSA and TL_{CO} and Vc, while BMI, which is included in many published reference equations, is correlated with all spirometric variables [37].

Accepted manuscript

The most commonly used reference equations are from studies in Dutch children [7], which are based on height only and fail to accurately describe the complex changes in pulmonary function during puberty [24]. Our results suggest that there are increases in pulmonary capacity as children grow from the ages of 8 to 14. Our study provides normative pulmonary function data (TLco, TL_{NO}, Dm, Vc and VA) in North African children using a standardized single-breath technique. Determination of Dm and Vc using $TL_{CO/NO}$ requires a single respiratory maneuver and allows simultaneous of TL_{CO}, TL_{NO}, as well as calculation of TL_{NO}/TL_{CO}, Dm and Vc.

In addition, $TL_{NO/CO}$ maneuver; generally, involves a shorter breath-hold due to the rapid disappearance of NO; is particularly suitable for infants and the rebreathing, required more cooperation, and could be performed in subjects with lower lung volumes.

Kim and al, 2012 said that the single-breath TLco technique can be challenging in young children and there have been attempts to perform easier techniques to mesure Tlco in children by using methods other than ATS/ERS guideline. However, results by other methods cannot be compared to the result using the single breath-hold maneuver, which can be easily performed by older children and adults.

Despite, the similarities in the performed pulmonary maneuver TLNO/CO and TLCO are two distinctly separate methods, with methodological differences

In our study the success rate of breath maneuver in young children was acceptable and highlights the value of experienced pediatric respiratory technicians in our laboratory. The present research was a prospective one, but was a cross-sectional study. Ideally, following children over time and measuring $TL_{NO/CO}$ longitudinally would generate more accurate reference values. However, reference equations for $TL_{NO/CO}$ in children are scarce compared to the more frequently used outcomes of TL_{CO}.

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Despite interesting recent studies [20;38] using the method of double transfer of NO/CO in children, the calculated of TL_{NO} in pediatric groups is currently restricted due to the lack of references values.

The reference equations in our study were not age dependent, but were influenced by weight and height, similar to findings in children from the Netherlands [7]. The Global Lung Function Initiative [12] for TL_{CO} suggests that non-linear approaches improve TL_{CO} predictive values (including in children), with recent confirming data on predicting TL_{CO} in a Brazilian population [39].

Our study is limited to data from 8-14-year-old Tunisians boys. These data should be expanded to include other age groups (younger and older boys and girls) to better explain the relationship between age, puberty and lung function.

Conclusions

We report the first set of predictive equations for pulmonary diffusing capacity in healthy young Tunisian boys. Our study demonstrates that TL_{NO} and TL_{CO} increases with height and body weight. Values for TL_{CO} in young Tunisian boys are higher than those in European children. We suggest that the predictive equations for pulmonary function are also suitable for use in other North African countries with similar populations.

Acknowledgements

The authors would like to thank children and parents for their enthusiastic participation in this research.

Conflicts of interest

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The authors declare no conflict of interest.

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References

1- Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CP, Gustafsson P, Hankinson J, Jensen R, Johnson DC, MacIntyre N, McKay R, Miller MR, Navajas D, Pedersen OF, Wanger J. Interpretative strategies for lung function tests. Eur Respir J. 2005 Nov;26(5):948-68.

2- Ginsberg JP1, Aplenc R, McDonough J, Bethel J, Doyle J, Weiner DJ. Pre-transplant lung function is predictive of survival following pediatric bone marrow transplantation. Pediatr Blood Cancer. 2010 Mar;54(3): 454-60.

3- Kim Y-J, Christoph K, Yu Z, Eigen H, Tepper RS. Pulmonary Diffusing Capacity in Healthy African-American and Caucasian Children. Pediatric Pulmonology 51:84–88 (2016).

4- Kim Y-J, Hall GL, Christoph K, Tabbey R, Yu Z, Tepper RS, Eigen H. Pulmonary Diffusing Capacity in Healthy Caucasian Children. Pediatric Pulmonology 47:469–475 (2012).

5- Cotes JE. Dabbs JM. Hall AM. Axford AT. Laurence KM: Lung volumes. ventilatory capacity and transfer factor in healthy British boy and girl twins. Thorax 1973; 28:709–715.

6- Ong KK, Ahmed ML, Dunger DB. Lessons from large population studies on timing and tempo of puberty (secular trends and relation to body size): the European trend. Mol Cell Endocrinol 2006; 254-255:8-12.

7- Koopman M. Zanen P. Kruitwagen CL. Van der Ent CK. Arets HG. Reference values for paediatric pulmonary function testing: The Utrecht dataset. Respiratory Medicine 2011: 105. 15-23.

8- American Thoracic Society Statement Snowbird workshop on standardisation of spirometry. Am Rev Respir Dis 1979; 119: 831-838.

Accepted manuscript

9- Quanjer PH. Borsboom GJ. Brunekreef B. Zach M. Forche G. Cotes JE. Sanchis J. Paoletti P. Spirometric reference values for white European children and adolescents: polgar revisited. Pediatr Pulmonol 1995; 19:135-42.

10- Stanojevic S. Wade A. Stocks J. Hankinson J. Coates AL. Pan H. Rosenthal M. Corey M. Lebecque P. Cole TJ. Reference ranges for spirometry across all ages: a new approach. Am J Respir Crit Care Med 2008; 177:253-60.

11- Stocks J, Quanjer PH. Reference values for residual volume, functional residual capacity and total lung capacity. ATS work-shop on lung volume measurements. Official statement of the European Respiratory Society. Eur Respir J 1995. 8/492-506.

12- Stanojevic S, Graham BL, Cooper BG, Thompson BR, Carter KW, Francis RW, Hall GL. Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians. Global Lung Function Initiative TLCO working group; Global Lung Function Initiative (GLI) TLCO. Eur Respir J. **2017** Sep 11;50(3).

13- Rosenthal M. Cramer D. Bain SH. Denison D. Bush A. Warner JO. Lung function in white children aged 4 to 19 years: II-single breath and plethysmography. Thorax 1993; 48:803-8.

14- Caussade S. Pulgar D. Vega-Briceno L. Viviani P. Diaz C. Contreras I. Sanchez I. Plethysmographic lung volumes in normal Chilean children and adolescents. Pediatr Pulmonol 2008; 43:866-73.

15- Ip MS. Karlberg EM. Chan KN. Karlberg JP. Luk KD. Leong JC. Lung function reference values in Chinese children and adolescents in Hong Kong. II. Prediction equations for plethysmographic lung volumes. AM j Respir Crit Care Med 2000; 162:430-5.

Accepted manuscript

16- Kaditis AG. Gourgoulianis K. Tsoutsou P. Papaioannou AI. Fotiadou A. Messini C. Samaras K. Piperi M. Gissaki D, Zintzaras E. Molyvdas AP. Spirometric values in Gypsy (Roma) children. Respiratory Medicine 2008; 102, 1321-28.

17- Alexandraki S, Koutsilieris M, Stafakas N, Katsardis C. Spirometric reference values in Greek children and adolescents. In Vivo 24: 195-200 (2010).

18- Ma Y-N, Wang J, Dong G-H, Liu M-M, Wang D, Liu Y-Q, Zhao Y, Ren W-H, Lee YL, Zhao Y-D, He Q-C. Predictive Equations Using Regression Analysis of Pulmonary Function for Healthy Children in Northeast China. PLoS One. 2013; 8(5): e63875.

19- Yang TS. Peat J. Keena V. Donnelly P. Unger W. Woolcock A. A review of racial differences in the lung function of normal Caucasian, Chinese and Indian subjects. Eur Respir J 1991; 4: 872-80

20- Dridi R. Glénet S. Tabka Z. Amri M. Guénard H: Effects of a basketball activity on lung capillary blood volume and membrane diffusing capacity measured by NO/CO transfer in children. Journal of Sports Science and Medicine 2006; 5: 431-439.

21- Ferris BG: Epidemiology standardisation project II: Recommended respiratory disease: questionnaire for use with adult and children in epidemiological research. Am Rev Resp Dis 1978; 118: 7-53.

22- Guénard H. Varene N. Vaida P: Determination of lung capillary blood volume and membrane diffusing capacity in man by the measurements of NO and CO transfer. Respiration Physiology 1987; 70: 113-120.

23- Forster R. Exchange of gases between alveolar air and pulmonary capillary blood: pulmonary diffusing capacity. Physiol Rev 1957; 37:391-452.

Accepted manuscript

24- DeGroodt EG. Van Pelt W. Borsboom GJ. Quanjer PH. Van Zomeren BC: Growth of lung and thorax dimensions during the pubertal growth spurt. Eur Respir J 1988; Feb:1(2):102-8.

25- Balinotti JE. Chakr VC. Tiller C. Kimmel R. Coates C. Kisling J. Yu Z. Nguyen J. Tepper RS: Growth of lung parenchyma in infants and toddlers with chronic lung disease of infancy. Am J Respir Crit Care Med (2010); 15:181(10):1093-7.

26- Hibbert EM. Couriel MJ. Landau IL: Changes in lung, airway and chest wall function in boys and girls between 8 and 12 years. J Appl Physiol 57 (1984): 304-308.

27- Hancox RJ. Poulton R. Greene JM. McLachlan CR. Pearce MS. Sears MR : Associations between birth weight, early childhood weight gain and adult lung function. Thorax 2009; Mar: 64(3):228-32.

28- Krawiec JA. Forster RE. Gottliebsen TW. Fish D: Rate of CO uptake by human red blood cells. Federation Proc 1983; 42: 993.

29- Trabelsi Y. Ben Saad H. Tabka Z. Gharbi N. Bouchez Buvry A. Richalet JP. Guénard H: Spirometric reference values in Tunisian children. Respiration 2004; Sep-Oct :71(5):511-8.

30- Roca J. Rodriguez-Roisin R. Cobo E. Burgos F. Perez J. Clausen JL: Single-breath carbon monoxide diffusing capacity prediction equations from a Mediterranean population. Am Rev Respir Dis 1990; 141: 1026-32.

31- Giammona STJ. Daly WJ: Pulmonary diffusing capacity in normal children. ages 4 to 13. Amer J Dis Child 1965; 110: 144-53.

32- Turley KR. Wilmore JH: Cardiovascular responses to submaximal exercise in 7- to 9-yr-old boys and girls. Med Sci Sports Exerc 1997; Jun : 29(6):824-32.

33- Maksud MG. Coutts KD. Hamilton LH: Oxygen uptake. ventilation. and heart rate. Study in Negro children during strenuous exercise. Arch Environ Health 1971; 23(1): 23-8.

Accepted manuscript

34- Andreacci JL. Robertson RJ. Dubé JJ. Aaron DJ. Balasekaran G. Arslanian SA: Comparison of maximal oxygen consumption between black and white prepubertal and pubertal children. Pediatr Res 2004; 56 (5):706-13.

35- Binyildiz PO: Prediction of maximal oxygen uptake in boys 11-13 years of age. Eur J Appl Physiol Occup Physiol 1980; 43(3):213-9.

36- Stam H. Van den Beek A. Grünberg K. Stijnen T. Tiddens HA. Versprille A. Pulmonary diffusing capacity at reduced alveolar volumes in children. Pediatr Pulmonol 1996 Feb; 21(2) :84-9.

37- Pistelli F. Bottai M. Viegi G. Di Pede F. Carrozzi L. Baldacci S. Pedreschi M. Giuntini C. Smooth reference equations for slow vital capacity and flow-volume curve indexes. Am J Respir Crit Care Med 2000; 161:899-905.

38- Thomas A, Hanel B, Marott JL, Buchvald F, Mortensen J, Nielsen KG. The single-breath diffusing capacity of CO and NO in healthy children of European descent. PLoS One. 2014 Dec 16;9(12).77.

39- Guimarães VP. Miranda DM. Reis MAS. Andrade TL. Matos RL. Soares MR. Pereira CAC. Reference values for the carbon monoxide diffusion (transfer factor) in a brazilian sample of white race. J Bras Pneumol. 2019: Oct 17;45(5).

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Tables and Figures list:

Tables:

Table 1. Mean and SD of anthropometric and pulmonary variables in healthy Tunisian boys.

Table 2. Regression relationships for prediction of Dm, TL, Vc and VA using standing height and weight in Tunisian children.

Table 3. Predicted diffusing capacity outcomes from this study and published data for children.

Figures:

Figure. 1. VA plotted against weight (**A**); TLco plotted against weight (**B**) and Vc plotted against weight (**C**).

Figure. 2. VA plotted against height (**A**); TL_{NO} plotted against height (**B**) and Dm plotted against height (**C**).

Figure 3 Relationship between: **A**) Dm and BSA; **B**) TLNO and BSA; **C)** TLco and BSA; **D**) Vc and BSA.

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	N	Mean ± SD	Minimum	Maximum
Age *(years)*	118	11.2 ± 1.3	8	14
Weight *(kg)*	118	41 ± 8.5	25	64
Height *(cm)*	118	149.5 ± 9	126	170
TL_{NO} *($mL.\ min^{-1}.\ mmHg^{-1}$)*	118	89.25 ±17.5	52.01	132.30
TLco *($mL.\ min^{-1}.\ mmHg^{-1}$)*	118	17.22 ± 3.8	9.75	32.10
Dm *($mL.min^{-1}.mmHg^{-1}$)*	118	45.51 ± 9.05	26.40	67.10
Vc *(mL)*	118	48.24 ± 13.4	23.05	88.90
VA *(L)*	118	3.55 ± 0.75	1.98	5.20

Table 1. Mean and SD of anthropometric and pulmonary variables in healthy Tunisian boys

Dependents Variable	N	Constant	Coefficient of the height	Coefficient of the weight	R^2	p
Dm ($mL.min^{-1}.mmHg^{-1}$)	118	-12.555	0.388		0.69	<0.01
VA (L)	118	-3.951	0.34		0.61	<0.01
TL_{NO} ($mL.\ min^{-1}\ mmHg^{-1}$)	118	-24.383	0.76		0.70	<0.01
VA (L)	118	-2.487		0.023	0.74	<0.01
TLco ($mL.\ min^{-1}\ mmHg^{-1}$)	118	8.979		0.201	0.64	<0.01
Vc (mL)	118	23.041		0.615	0.79	<0.01

Table 2. Regression relationships for prediction of Dm, TL, Vc and VA using standing height and weight in Tunisian children.

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Study	TL_{CO} (ml/min/mmHg)	VA (L)
This study	17.22 ± 3.8	3.55 ± 0.75
Koopman and al, 2011 Boy's Age (yrs):7 Height (cm):120	13,57	2,05
Kim and al, 2016 * *Caucasian children* N:301/Age(yrs) :12,19(3,01) Height(cm):153,45(16,53)	20,54 ± 6,74	3,87 ± 1,38
* *African-American children* N:151/Age(yrs) :12,42(3,45) Height(cm):153,30(18,60)	19,22 ± 6,77	3,51 ± 1,41
Kim and al, 2012 N:479/Age(yrs) :12(3,1) Height(cm):152,3(17,4) Weight(kg) :46,8(16,7)	19,93 ± 6,64	3,74 ± 1,35
Stam and al, 1996 Boy's Age (yrs):7 Height(cm) :120	11,20	Not reported
Rosenthal and al, 1993 Boy's Age (yrs):7 Height(cm) :120	13,17	1,74

Table 3. Predicted diffusing capacity outcomes from this study and published data for children

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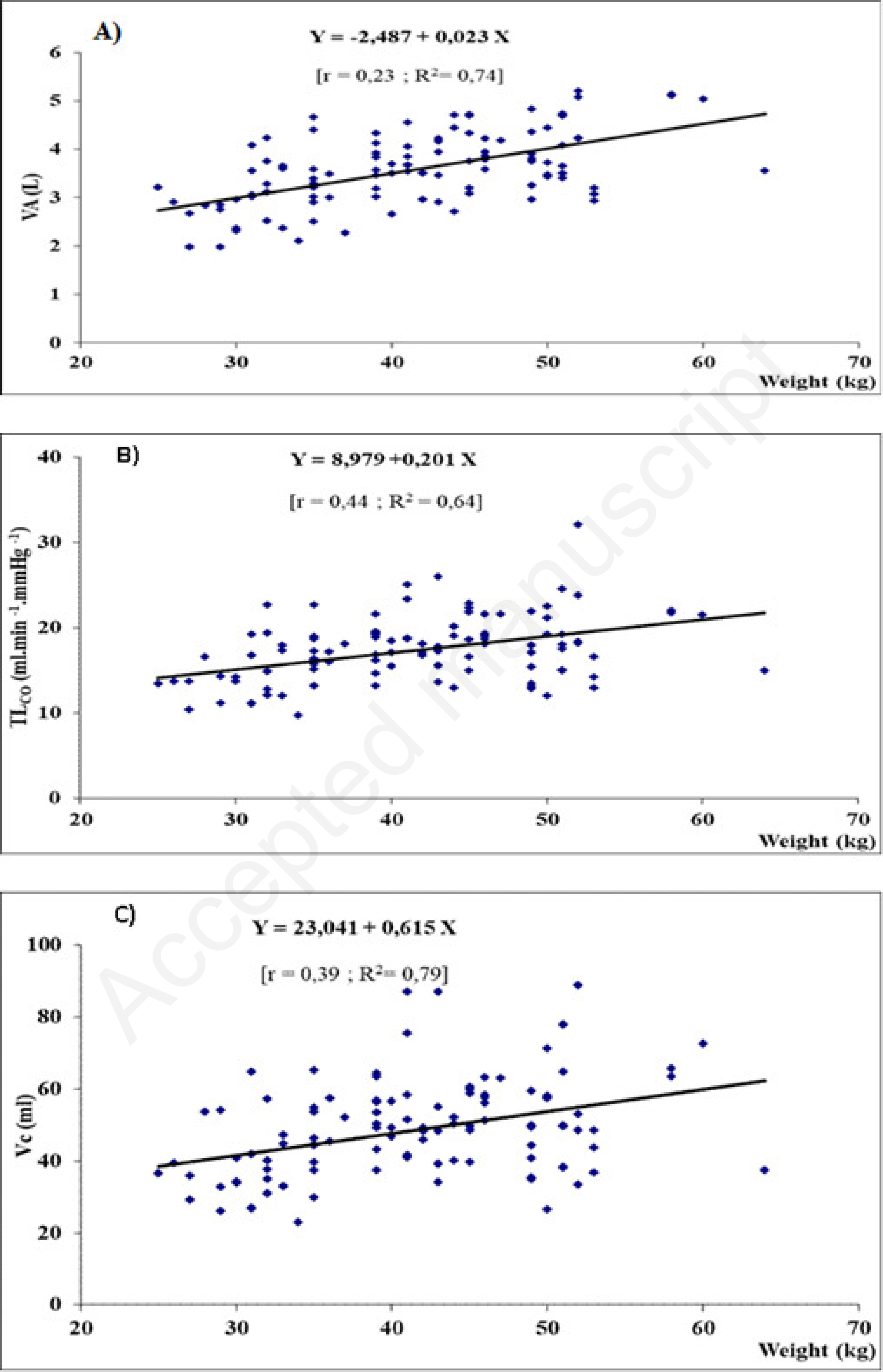

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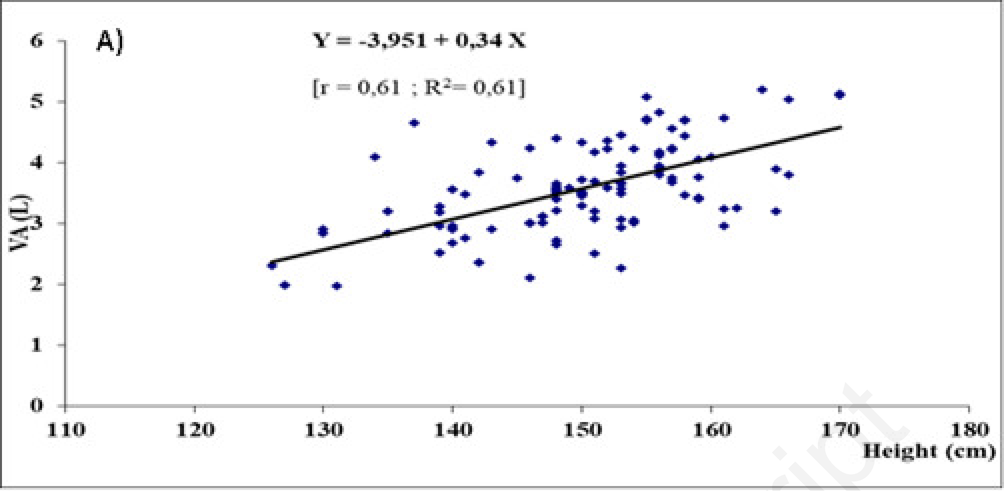

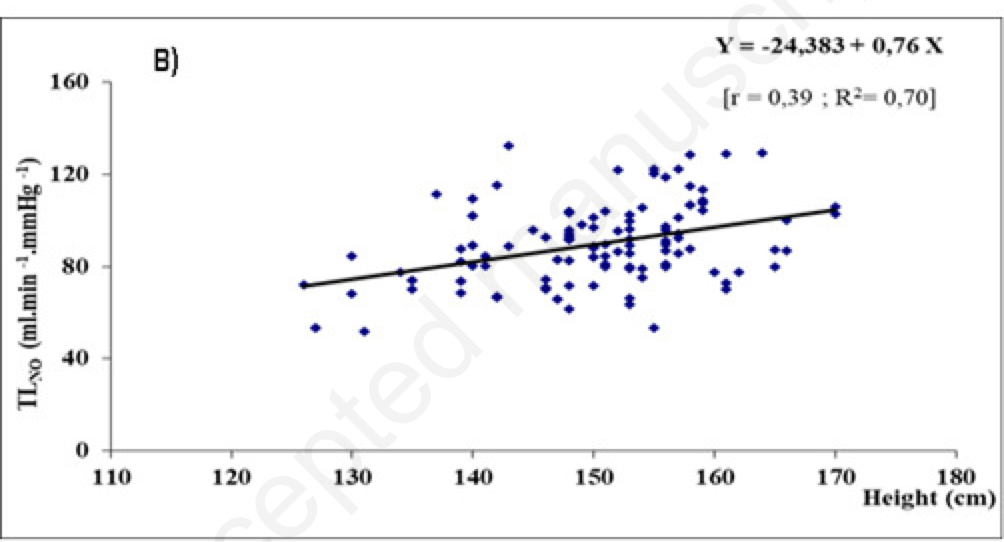

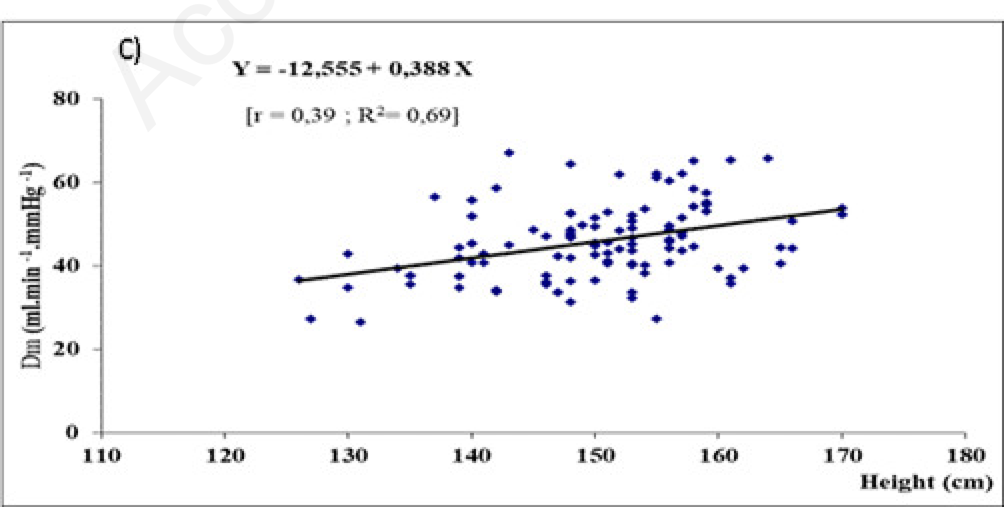

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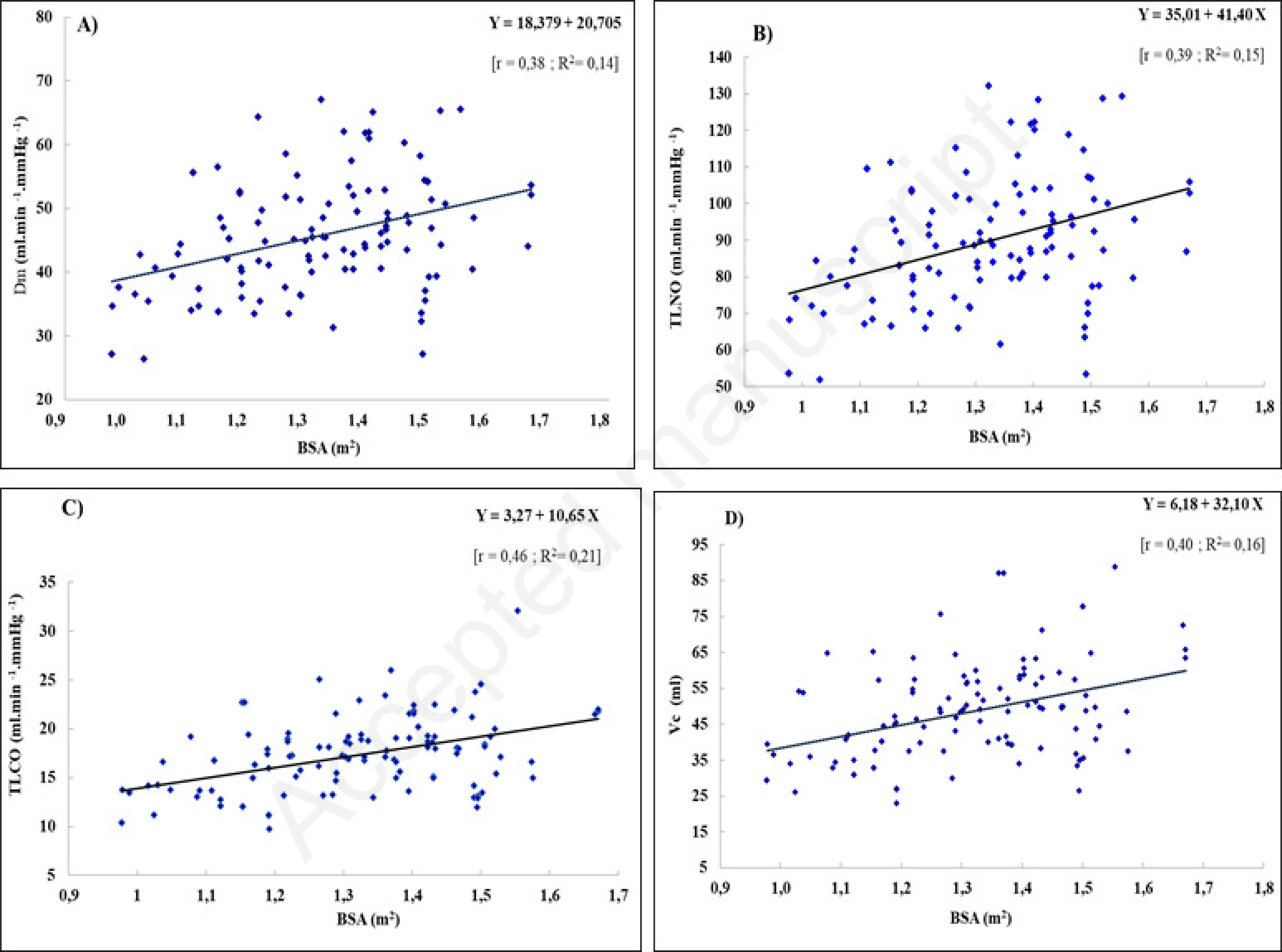

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