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Journal of Sport and Health Science 8 (2019) 183–188

www.jshs.org.cn

Original article

Determinants of inspiratory muscle function in healthy children

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Received 8 April 2016; revised 24 May 2016; accepted 5 July 2016

Available online 3 August 2016

Abstract

Background: Children are affected by disorders that have an impact on the respiratory muscles. Inspiratory muscle function can be assessed by means of the noninvasive tension–time index of the inspiratory muscles (TTI_{mus}). Our objectives were to identify the determinants of TTI_{mus} in healthy children and to report normal values of TTI_{mus} in this population.

Methods: We measured weight, height, upper arm muscle area (UAMA), and TTI_{mus} in 96 children aged 6–18 years. The level and frequency of aerobic activity was assessed by questionnaire.

Results: TTI_{mus} was significantly lower in male subjects (0.095 ± 0.038, mean ± SD) compared with female subjects (0.126 ± 0.056) ($p = 0.002$). TTI_{mus} was significantly lower in regularly exercising (0.093 ± 0.040) compared with nonexercising subjects (0.130 ± 0.053) ($p < 0.001$). TTI_{mus} was significantly negatively related to age ($r = -0.239$, $p = 0.019$), weight ($r = -0.214$, $p = 0.037$), height ($r = -0.355$, $p < 0.001$), and UAMA ($r = -0.222$, $p = 0.030$). Multivariate logistic regression analysis revealed that height and aerobic exercise were significantly related to TTI_{mus} independently of age, weight, and UAMA. The predictive regression equation for TTI_{mus} in male subjects was $TTI_{mus} = 0.228 - 0.001 \times$ height (cm), and in female subjects it was $TTI_{mus} = 0.320 - 0.001 \times$ height (cm) .

Conclusion: Gender, age, anthropometry, skeletal muscularity, and aerobic exercise are significantly associated with indices of inspiratory muscle function in children. Normal values of TTI_{mus} in healthy children are reported.

Keywords: Aerobic exercise; Children; Inspiratory muscle function; Maximal inspiratory pressure; Skeletal muscle function; Tension–time index of the inspiratory muscles

1. Introduction

Respiratory muscle impairment has been increasingly recognized as an independent pathophysiological contributor to disorders that affect the pediatric population. Children with cystic fibrosis (CF)[1–3] and neuromuscular diseases[4] are at increased risk of respiratory muscle fatigue. Obese individuals have impaired respiratory muscle function compared with controls owing to increased mechanical loading of the respiratory muscles.[5] Impaired respiratory muscle function has been identified as an independent predictor of extubation outcome in children.[6] Furthermore, anthropometry,[7] genetic polymorphisms,[8] and aerobic exercise[9,10] also contribute to respiratory muscle function in children.

Respiratory muscle strength can be noninvasively determined by the measurement of the maximal inspiratory pressure (P_{Imax}) and the maximal expiratory pressure (P_{Emax}).[11] Although P_{Imax} and P_{Emax} describe a snapshot of respiratory muscle performance at a specific time point, respiratory muscle function and the risk for muscle fatigue can be better assessed by indices that additionally describe the respiratory load, which consists of the chest wall and lung elastic loads plus the resistive loads. Such an index is the noninvasive tension–time index of the inspiratory muscles (TTI_{mus}).[12] TTI_{mus} is a composite dimensionless index that incorporates measurements of pressure and time and describes the efficiency of the total work undertaken by the respiratory muscles.[13] Higher values of TTI_{mus} are indicative of inefficient inspiratory muscle function and increased risk of inspiratory muscle fatigue and respiratory failure.[12,13]

Clinical assessment of the relative risk of inspiratory muscle fatigue and respiratory failure in children may facilitate decisions aimed at either instituting treatment modalities such as

Peer review under responsibility of Shanghai University of Sport.

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https://doi.org/10.1016/j.jshs.2016.08.002

Cite this article: Dassios T, Dimitriou G. Determinants of inspiratory muscle function in healthy children. *J Sport Health Sci* 2019;8:183–8.

noninvasive ventilation and inspiratory muscle training or implementing strategies for weaning from mechanical ventilation.

To our knowledge, studies reporting values of TTI_{mus} in healthy children are scarce,[7] and patient-derived data and data from ventilated subjects would be affected by distorted lung mechanics. In this study we describe patterns of change of TTI_{mus} in healthy children and report the demographic and anthropometric parameters that contribute to alterations of inspiratory muscle function in this population.

2. Methods

2.1. Subjects

Ninety-six healthy children without respiratory problems who were able to perform reproducible maximal respiratory maneuvers were prospectively recruited. They were studied in the outpatient department of the University Hospital of Patras, Greece. Their age ranged from 6 to18 years. The subjects were healthy children recruited from the community and siblings of children attending the outpatient department. Children with pre-existing respiratory conditions such as asthma or CF, children with genetic disorders such as thalassemia, and children who were unwell were excluded from the study. Children younger than 6 years of age were excluded because they could not reliably execute reproducible maneuvers requiring a maximal effort. Suitability of inclusion was assessed by questionnaire.

All respiratory and nutrition measurements were performed by the same examiner (TD). The study protocol was approved by the Research Ethics Committee of the University Hospital of Patras. Parents or legal guardians provided informed written consent prior to the study, and children provided informed assent.

2.2. Measurements

2.2.1. Equipment

A pneumotachograph (Mercury F100L; GM Instruments, Kilwinning, UK) was used to record airway flow. This was connected to a differential pressure transducer (DP45, range ±3.5 cmH_2O; Validyne Engineering, Northridge, CA, USA). A side port on the pneumotachograph connected to a differential pressure transducer (DP45, range ±225 cmH_2O) was used to measure airway pressure. The signals from the differential pressure transducers were amplified by a portable amplifier (Validyne CD280; Validyne Engineering). The flow and pressure signals were recorded and displayed in real time on a portable computer (Dell GX620; Dell Inc., Round Rock, TX, USA) running a LabVIEW application (National Instruments, Austin, TX, USA). Analog to digital sampling was at 100 Hz (16-bit NI PCI-6036E; National Instruments).

2.2.2. Measurement of the respiratory pressures

Respiration rate, tidal volume, airway pressure generated 0.1 s after an occlusion ($P_{0.1}$), P_{Imax}, P_{Emax}, inspiratory time (T_i), and total time of respiration (T_{tot}) were measured for each participating subject. Minute ventilation was calculated as the product of tidal volume times respiratory rate. $P_{0.1}$ was calculated as the airway pressure generated 100 ms after an occlusion while the subject was breathing quietly. A minimum of 4 airway occlusions were undertaken, and the average $P_{0.1}$ value was estimated.[11] A rubber mouthpiece (dead space 3.5 mL) was pressed tightly against the lips, and the respiratory circuit was occluded at the end of expiration. Any leak around the mouthpiece was minimized. The occlusions were performed with a unidirectional valve (dead space 8 mL) connected to the mouthpiece. P_{Imax} was measured on a maximal inspiratory effort from residual volume against an occluded airway, and P_{Emax} was measured on a maximal expiratory effort from total lung capacity against an occluded airway.[14] Five maximal reproducible respiratory efforts were undertaken, and the maximum achieved values for P_{Imax} and P_{Emax} were recorded.[14] A 1–2 mm leak in the respiratory line was allowed to avoid closure of the glottis.[11] Only P_{Imax} and P_{Emax} waveforms with minimum plateau pressure of 1 s were accepted for subsequent analysis.[11]

2.2.3. Calculation of the TTI_{mus}

The TTI_{mus} was calculated as

$$TTI_{mus} = (P_{Imean} / P_{Imax}) \times (T_i / T_{tot}),$$

where T_i is the inspiration time and T_{tot} is the total time for each breath, calculated from the airway flow signal; P_{Imean} is the mean airway pressure during inspiration (calculated from the formula $P_{Imean} = 5 \times P_{0.1} \times T_i$); and P_{Imax} is the maximum inspiratory pressure.[3,12]

2.3. Nutritional parameters

Body weight and height were measured, and the body mass index (BMI) *Z*-score was calculated.[15] Because respiratory muscle function is strongly associated with indices of somatic muscularity,[1,3] the upper arm muscle area (UAMA) was measured; midarm muscle circumference was measured midway between the olecranon process and the tip of the acromion with the right hand hanging relaxed.[16] Triceps skinfold thickness was measured by a Harpenden Skinfold Caliper (Baty International, West Sussex, UK) halfway over the triceps muscle and with the skinfold parallel to the longitudinal axis of the humerus.[16] UAMA was subsequently calculated from midarm muscle circumference and triceps skinfold thickness.[17]

2.4. Exercise

The level of physical activity (PA) was evaluated with a questionnaire. The exercise group was formed by subjects who engaged in moderate-to-vigorous aerobic activity a minimum of 3 times per week, 45 min each time, over the past 3 months.[10,18,19] Running, cycling, football, swimming, athletics, basketball, volleyball, martial arts, tennis, and gymnastics were accepted as moderate-to-vigorous PA.[19] The control group consisted of subjects who did not take part in structured PA.

2.5. Statistics

Normality of distribution was assessed using the Shapiro-Wilk and Kolmogorov-Smirnoff tests. Differences between 2

groups were assessed for significance using the student's *t* test. Pearson correlation analysis was used to examine the univariate relation of $P_{0.1}$, P_{Imax}, and TTI_{mus} to age, weight, height, BMI *Z*-score, and UAMA. Multivariate logistic regression was performed to determine which variables contribute to alterations of TTI_{mus}. Regression equations for predictive values of TTI_{mus} in males and females were calculated with the corresponding coefficient of determination (R^2) and standard error of the estimate. A *p* value of <0.05 was accepted as significant. Multicollinearity among the independent variables in the regression analysis was assessed by calculation of the tolerance for the independent variables. A retrospective sample size justification was conducted to confirm that the number of participating subjects in the exercising and nonexercising groups were sufficient to detect differences in TTI_{mus} at a level of significance of 0.01 with power of 95%. Statistical analysis was performed using SPSS software (Version 17.0; SPSS Inc., Chicago, IL, USA).

3. Results

All recruited subjects were able to complete the respiratory measurements and the nutrition assessment. Power analysis was conducted to assess the sample size required to identify TTI_{mus} differences between the groups of exercising and nonexercising subjects. TTI_{mus} standard deviation was set at 0.014.[3] The power analysis indicated that to detect an increase in TTI_{mus} of 0.016[1] at a power of 95% and a level of statistical significance of 0.01, a sample size of at least 32 subjects was required for each group. Anthropometric, nutrition, and respiratory function data in male and female subjects are presented in Table 1. P_{Imax} ($p = 0.043$) and P_{Emax} ($p = 0.001$) were significantly higher in male subjects compared with female subjects. P_{Imean}/P_{Imax} and TTI_{mus} were significantly lower in male subjects compared with female subjects ($p = 0.001$ and $p = 0.002$, respectively). Values of P_{Imax} and TTI_{mus} in different age groups in males and females are presented in Table 2. Respiratory function data in exercising and nonexercising participants are presented in Table 3. P_{Imax} and P_{Emax} were significantly higher in exercising compared with nonexercising subjects ($p = 0.002$ and $p = 0.015$, respectively). TTI_{mus} was significantly lower in exercising compared with nonexercising subjects ($p < 0.001$).

$P_{0.1}$ was significantly negatively related to age ($r = -0.415$, $p < 0.001$), weight ($r = -0.245$, $p = 0.016$), height ($r = -0.386$, $p < 0.001$; Fig. 1A), and UAMA ($r = -0.222$, $p = 0.029$) but not significantly related to BMI *Z*-score. P_{Imax} was significantly related to weight ($r = 0.221$, $p = 0.031$), height ($r = 0.320$, $p = 0.001$; Fig. 1B), and UAMA ($r = 0.201$, $p = 0.049$) but not significantly related to age and BMI *Z*-score. TTI_{mus} was significantly negatively related to age ($r = -0.239$, $p = 0.019$), weight ($r = -0.214$, $p = 0.037$), height ($r = -0.355$, $p < 0.001$; Fig. 1C), and UAMA ($r = -0.222$, $p = 0.030$) but not significantly related to BMI *Z*-score. Multivariate logistic regression analysis revealed that height ($p = 0.004$) and aerobic exercise ($p = 0.002$) were significantly related to TTI_{mus} independently of age, weight, and UAMA (Table 4).

Table 1
Anthropometric, nutrition, and respiratory muscle function data in male and female participants (mean ± SD).

	Male ($n = 48$)	Female ($n = 48$)	*p*
Age (year)	12 ± 3	12 ± 3	0.800
Age 6–12 years (*n* (%))	26 (54)	26 (54)	1.000[a]
Height (cm)	158 ± 16	153 ± 14	0.105
Weight (kg)	53 ± 19	49 ± 13	0.149
BMI *Z*-score	0.66 ± 0.87	0.49 ± 0.88	0.347
TST (mm)	14 ± 5	16 ± 5	0.026
MAMC (cm)	24.9 ± 4.2	24.1 ± 2.9	0.276
UAMA	3455 ± 1097	2918 ± 609	0.004
RR	21 ± 5	20 ± 5	0.514
TV (L)	0.56 ± 0.23	0.61 ± 0.23	0.026
TV/kg (mL/kg)	10.9 ± 4.3	13.2 ± 5.8	0.268
MV (L/min)	11.2 ± 3.9	12.0 ± 4.5	0.026
$P_{0.1}$ (cmH_2O)	2.75 ± 1.11	3.15 ± 1.42	0.134
P_{Imean} (cmH_2O)	17.3 ± 6.0	20.9 ± 9.1	0.028
P_{Imax} (cmH_2O)	87 ± 27	76 ± 23	0.043
P_{Imean}/P_{Imax}	0.22 ± 0.09	0.29 ± 0.12	0.001
T_i/T_{tot}	0.44 ± 0.02	0.44 ± 0.03	0.203
TTI_{mus}	0.095 ± 0.038	0.126 ± 0.056	0.002
P_{Emax} (cmH_2O)	90 ± 27	75 ± 19	0.001
Sport (*n* (%))	27 (56)	21 (44)	0.683[a]

[a] χ^2.
Abbreviations: BMI *Z*-score = body mass index *Z*-score; MAMC = midarm muscle circumference; MV = minute ventilation; $P_{0.1}$ = inspiratory pressure 100 ms after onset of inspiration; P_{Emax} = maximal expiratory pressure; P_{Imax} = maximal inspiratory pressure; P_{Imean} = mean airway pressure during inspiration; RR = respiratory rate; T_i = inspiratory time; TST = triceps skinfold thickness; TTI_{mus} = tension–time index of the respiratory muscles; T_{tot} = total time of respiration; TV = tidal volume; TV/kg = tidal volume per kilogram of body weight; UAMA = upper arm muscle area.

Table 2
Mean values of P_{Imax} and TTI_{mus} according to age in males and females (mean ± SD).

Age (year)	Male			Female		
	n	P_{Imax} (cmH_2O)	TTI_{mus}	*n*	P_{Imax} (cmH_2O)	TTI_{mus}
6–8	7	79 ± 20	0.118 ± 0.042	7	75 ± 27	0.167 ± 0.049
9–11	13	79 ± 28	0.112 ± 0.040	11	77 ± 27	0.135 ± 0.060
12–14	17	94 ± 25	0.089 ± 0.031	19	78 ± 22	0.127 ± 0.040
15–18	11	95 ± 31	0.076 ± 0.040	11	75 ± 21	0.106 ± 0.057

Abbreviations: P_{Imax} = maximal inspiratory pressure; TTI_{mus} = tension–time index of the respiratory muscles.

Table 3
Respiratory function data in exercising and nonexercising participants (mean ± SD).

	Exercise ($n = 50$)	Nonexercise ($n = 46$)	*p*
Age (year)	13 ± 3	12 ± 3	0.061
TV/kg (mL/kg)	11.7 ± 4.1	12.5 ± 6.2	0.469
MV (L/min)	12.0 ± 4.2	11.1 ± 4.1	0.275
$P_{0.1}$ (cmH_2O)	2.69 ± 1.13	3.23 ± 1.40	0.041
P_{Imax} (cmH_2O)	89 ± 26	74 ± 23	0.002
T_i/T_{tot}	0.44 ± 0.03	0.44 ± 0.03	0.395
TTI_{mus}	0.093 ± 0.040	0.130 ± 0.053	<0.001
P_{Emax} (cmH_2O)	89 ± 24	76 ± 24	0.015
Male *n* (%)	27 (54)	21 (46)	0.688[a]

[a] χ^2.
Abbreviations: MV = minute ventilation; $P_{0.1}$ = inspiratory pressure 100 ms after onset of inspiration; P_{Emax} = maximal expiratory pressure; P_{Imax} = maximal inspiratory pressure; T_i = inspiratory time; T_{tot} = total time of respiration; TTI_{mus} = tension–time index of the respiratory muscles; TV/kg = tidal volume per kilogram of body weight.

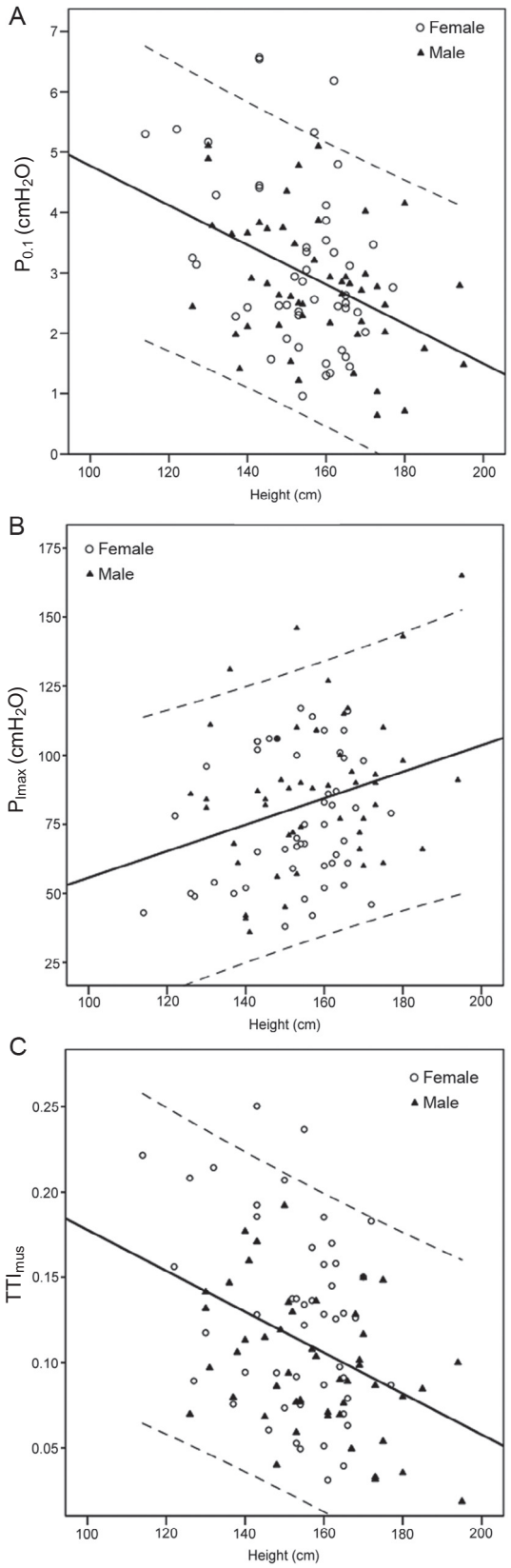

Fig. 1. $P_{0.1}$ (A), P_{Imax} (B), TTI_{mus} (C), and height linear regression analysis. Data for individual subjects, line of regression, and 95% confidence intervals are presented. $P_{0.1}$ = inspiratory pressure 100 ms after onset of inspiration; P_{Imax} = maximal inspiratory pressure; TTI_{mus} = tension–time index of the respiratory muscles.

Table 4
Multivariate regression analysis with TTI_{mus} as the outcome variable.

	Standardized coefficient (95%CI)	*p*
Age	0.124 (−0.003 to 0.007)	0.410
Weight	0.413 (0.000 to 0.003)	0.056
UAMA	−0.175 (0.000 to 0.000)	0.275
Aerobic exercise	−0.295 (−0.048 to −0.011)	0.002
Height	−0.606 (−0.003 to −0.001)	0.004

Abbreviations: CI = confidential confidence; TTI_{mus} = tension–time index of the respiratory muscles; UAMA = upper arm muscle area.

Predictive regression equations for TTI_{mus} were as follows:

Males: $TTI_{mus} = 0.228 - 0.001 \times \text{height (cm)}$;

Coefficient of determination: $R^2 = 0.401$, standard error of estimation: 0.037.

Females: $TTI_{mus} = 0.320 - 0.001 \times \text{height (cm)}$;

Coefficient of determination: $R^2 = 0.315$, standard error of estimation: 0.053.

4. Discussion

Our study demonstrated that inspiratory muscle function is enhanced in regularly exercising children compared with nonexercising ones. We reported that TTI_{mus} values are normal in healthy children and are negatively related to height, weight, age, and muscular state. Furthermore, we calculated predictive regression equations for TTI_{mus} in male and female children.

TTI_{mus} in our study attained comparable values to previously published data for nonventilated children.[1–4,7] Assessment of respiratory muscle function by means of TTI_{mus} has demonstrated that measurement of TTI_{mus} can accurately predict extubation outcome in ventilated children.[6] Children with CF exhibit increased TTI_{mus} values, signaling compromised respiratory muscle function, which is determined by a combination of increased load and decreased strength owing to airway obstruction and malnutrition, respectively.[1–3,20] Children with neuromuscular disorders also attain higher TTI_{mus} values, mainly secondary to decreased respiratory muscle strength as a direct consequence of the disease.[4] Obese individuals exhibit increased TTI_{mus} values as a result of the excessive mechanical load imposed on the respiratory muscles.[5] Our study reconfirmed the range of values of TTI_{mus} reported in previous studies and complemented the literature with novel, previously unreported parameters that determine TTI_{mus}, such as the state of skeletal muscularity and the effect of aerobic exercise on the respiratory muscles in healthy children. Given the reported impact of genetic polymorphisms on respiratory muscle function,[8] another strength of our study is that it is the first to report normal values of TTI_{mus} in healthy southern European, predominantly Greek, children.

Male children exhibited lower values of TTI_{mus} in our study compared with age-matched females. Male muscles are known to generate a higher maximum power output than female muscles. The mechanisms behind gender-related differences in

skeletal muscle function are not known, but they are likely a consequence of different sex hormonal status.[21]

Respiratory muscle function in children can be affected by increased respiratory load, decreased muscle strength, or a combination of both. Hence, TTI_{mus} is an index ideally equipped to describe and assess this compromise. Furthermore, TTI_{mus} is a global inspiratory muscle index that does not preferentially assess diaphragm function, and it is also noninvasive and simple to perform. Other methods have been utilized to assess respiratory muscle function, such as diaphragmatic electromyography[22] or sniff nasal inspiratory pressure (SNIP).[23] However, surface diaphragmatic electromyography in children would be considerably affected by electrical noise from neighboring muscle groups, whereas nostril occlusion for measurement of SNIP might be poorly tolerated in young children, and SNIP values might vary substantively for anatomic reasons in children of different ethnic backgrounds.[24]

Our study reported values of $P_{0.1}$ that decrease with age. $P_{0.1}$ is a reproducible index[25] that was introduced to assess respiratory drive in children with chronic intrinsic loaded breathing.[11,26] Although it is perceived that the timing of the $P_{0.1}$ is such that it is independent of lung compliance and airway resistance, the age-related decrease in $P_{0.1}$ in our study might reflect developmental changes, which is consistent with the tendency of lung compliance to increase through childhood into early adult life.[27]

In our study P_{Imax} increased with age; this probably reflects a maturation process related to increasing muscle mass and body growth.[28] Values of P_{Imax} have been previously reported in children.[23] Our study reports values for maximal respiratory pressures similar to previously published data from healthy children.[7,29–32] Both P_{Imax} and P_{Emax} positively correlated with increasing age and anthropometric indices that describe muscular state; given that respiratory muscles are skeletal muscles, this is a logical finding.

In terms of clinical significance, our data demonstrate that TTI_{mus} in children is influenced by gender, anthropometry, indices of muscularity, and aerobic exercise. Incorporating this information into clinical practice could enhance the use of TTI_{mus} as an objective monitoring parameter of inspiratory muscle function in children and could assist in predicting respiratory muscle fatigue in conjunction with clinical and pulmonary function data. Early recognition of impending respiratory failure would allow for timely application of treatment modalities such as noninvasive ventilation, inspiratory muscle training, and mechanical ventilation. The protective role of aerobic exercise in maintaining inspiratory muscle strength is reinforced by our results.

Assessment of inspiratory muscle function by the TTI_{mus} might be restricted by some potential limitations. In calculating the TTI_{mus}, P_{Imean} is extrapolated from $P_{0.1}$ over the entire T_i by a single power function of time, assuming that pressure increases linearly over T_i. In reality, this might overestimate the actual value of P_{Imean}. Furthermore, the critical fatigue isopleth for TTI_{mus} has been established by Ramonatxo et al.[12] to correspond to a specific fatigue threshold of the transdiaphragmatic pressure–time index, but the TTI_{mus} threshold itself has not been electromyographically determined in children.[13] Finally, in clinical practice, measurement of $P_{0.1}$ might be affected by the elevated time constant and the subsequent relatively delayed transmission of the pressure changes from the alveoli to the mouth in diseases characterized by airway obstruction, such as CF.[33]

We also acknowledge that although self-report data might be widely accepted, the validity of the study would have been enhanced if exercise journals approved by coaches or trainers had been used. Furthermore, our population—however sufficient to describe physiological associations—was relatively modest in size to generate predictive equations and did not undergo lung function testing to confirm that no individuals with impaired pulmonary function were included. Further research in this area might clarify whether certain forms of aerobic exercise in children might be more beneficial for respiratory muscle function than others.

5. Conclusion

This study demonstrated that inspiratory muscle function in healthy children is determined by height and that aerobic exercise might enhance respiratory muscle strength. This knowledge is essential to assess the respiratory muscles and to monitor respiratory muscle dysfunction and disease progression in children.

Acknowledgment

The statistical guidance of Dr. Richard Parker of the Center for Applied Medical Statistics, University of Cambridge, UK, is gratefully acknowledged.

Authors' contributions

TD contributed to study design, acquired and interpreted the data, and wrote the first draft of the manuscript; GD conceived of the study, contributed to study design and data interpretation, and critically appraised the manuscript. Both authors have read and approved the final manuscript, and agree with the order of presentation of the authors.

Competing interests

Both authors declare that they have no competing interests.

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