DOI:
10.1016/j.jshs.2016.08.002

HOSTED BY

ELSEVIER

Available online at www.sciencedirect.com

ScienceDirect

Journal of Sport and Health Science xx (2016) 1–6

www.jshs.org.cn

Original Article

Determinants of inspiratory muscle function in healthy children

Theodore Dassios [a,b,*], Gabriel Dimitriou [b]

[a] Department of Child Health, King's College Hospital, Denmark Hill, London, SE5 9RS, UK

[b] Department of Paediatrics, University of Patras Medical School, Patras, Rio 26504, Greece

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

Available online

Background: Children are affected by disorders that impact on the respiratory muscles. Inspiratory muscle function can be assessed by the non-invasive 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 to female subjects (0.126 ± 0.056) ($p = 0.002$). TTI_{mus} was significantly lower in regularly exercising (0.093 ± 0.040) compared to non-exercising 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. Predictive regression equation for TTI_{mus} in male subjects was: $TTI_{mus} = 0.228 - 0.001 \times \text{height (cm)}$, and in female subjects: $TTI_{mus} = 0.320 - 0.001 \times \text{height (cm)}$.

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 in disorders that affect the paediatric 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 to controls due 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 non-invasively determined by the measurement of the maximal inspiratory pressure (P_{Imax}) and the maximal expiratory pressure (P_{Emax}).[11] While 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 non-invasive Tension-Time Index of the inspiratory muscles (TTI_{mus}).[12] TTI_{mus} is a composite dimensionless index which 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 instituting treatment modalities such as noninvasive ventilation and inspiratory muscle training or at implementing strategies for weaning from mechanical ventilation.

Peer review under responsibility of Shanghai University of Sport.

* Corresponding author.

E-mail address: theodore.dassios@kcl.ac.uk (T. Dassios)

http://dx.doi.org/10.1016/j.jshs.2016.08.002

To our knowledge, studies reporting values of TTI_{mus} in healthy children are scarce,[7] while 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 outpatients department of the University Hospital of Patras, Greece. Their age ranged between 6 and 18 years. The subjects were healthy children recruited from the community and siblings of children attending the outpatients department. Children with preexisting respiratory conditions such as asthma or CF, children with genetic disorders such as thalassemia and children that were unwell were excluded from the study. Children younger than 6 years of age were excluded as 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 cm H_2O, Validyne Engineering, Northridge, CA, USA). A side port on the pneumotachograph, connected to a differential pressure transducer (DP45, range ± 225 cm H_2O) was used to measure airway pressure. The signals from the differential pressure transducers were amplified by a portable amplifier (Validyne CD 280; 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 (NI, Austin, TX, USA). Analog to digital sampling was at 100 Hz (16-bit NI PCI-6036E; NI).

2.2.2. Measurement of the respiratory pressures

Respiration rate (RR), tidal volume (TV), 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 TV times the RR. $P_{0.1}$ 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 minimised. The occlusions were performed with a unidirectional valve (dead space 8 mL) connected to the mouthpiece. P_{Imax} was measured upon a maximal inspiratory effort from Residual Volume against an occluded airway and P_{Emax} was measured upon a maximal expiratory effort from Total Lung Capacity against an occluded airway.[14] Five maximal reproducible respiratory efforts were undertaken and the maximum achieved value for P_{Imax} and P_{Emax} was 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 plateau pressure of minimum 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 Ti is the inspiration time and Ttot is the total time for each breath, calculated from the airway flow signal, P_{Imean} was the mean airway pressure during inspiration (calculated from the formula $P_{Imean} = 5 \times P_{0.1} \times T_i$) and P_{Imax} was 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] Since respiratory muscle function is strongly associated with indices of somatic muscularity,[1,3] the upper arm muscle area (UAMA) was measured: mid-arm muscle circumference (MAMC) was measured midway between the olecranon process and the tip of the acromion with the right hand hanging relaxed.[16] Triceps skinfold thickness (TST) 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 MAMC and TST.[17]

2.4. Exercise

The level of physical activity was evaluated with questionnaire. The exercise group was formed by subjects that engaged in moderate to vigorous aerobic activity for a minimum of 3 times per week, for 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 physical activity.[19] The control group consisted of subjects that did not take part in structured physical activity.

2.5. Statistics

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

Please cite this article in press as: Theodore Dassios, Gabriel Dimitriou, Determinants of inspiratory muscle function in healthy children, Journal of Sport and Health Science (2016), doi: 10.1016/j.jshs.2016.08.002

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. *P* values of <0.05 were 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 non-exercising 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 IBM SPSS Software (Version 17.0; IBM Corporation, Chicago, IL, USA).

3. Results

All recruited subjects were able to complete the respiratory measurements and nutrition assessment. Power analysis was conducted to assess the sample size required to identify TTI_{mus} differences between the groups of exercising versus non-exercising subjects. TTI_{mus} standard deviation was set at 0.014.[3] The power analysis indicated that in order 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 of subjects. 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 to female subjects. P_{Imean}/P_{Imax} and TTI_{mus} were significantly lower in male subjects compared to 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 non-exercising participants are presented in Table 3. P_{Imax} and P_{Emax} were significantly higher in exercising compared to non-exercising subjects ($p = 0.002$ and $p = 0.015$, respectively). TTI_{mus} was significantly lower in exercising compared to non-exercising 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* value
Age (year)	12 ± 3	12 ± 3	0.800
Age 6-12 years (%)	26 ± 54	26 ± 54	1.000*
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*

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

Predictive regression equations for TTI_{mus} were:

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 to non-exercising ones. We reported normal values of TTI_{mus} in healthy children and that TTI_{mus} values 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 non-ventilated 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 obstruc-

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

Age (year)	Male (*n*)		Female (*n*)	
	Pimax (cmH2O)	TTI_{mus}	Pimax (cmH2O)	TTI_{mus}
6-8	79 ± 20 (7)	0.118 ± 0.042 (7)	75 ± 27 (7)	0.167 ± 0.049 (7)
9-11	79 ± 28 (13)	0.112 ± 0.040 (13)	77 ± 27 (11)	0.135 ± 0.060 (11)
12-14	94 ± 25 (17)	0.089 ± 0.031 (17)	78 ± 22 (19)	0.127 ± 0.040 (19)
15-18	95 ± 31 (11)	0.076 ± 0.040 (11)	75 ± 21 (11)	0.106 ± 0.057 (11)

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

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

	Exercise (*n* = 50)	Non-exercise (*n* = 46)	*p* value
Age (years)	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 gender (%)	27 ± 54	21 ± 46	0.688*

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

tion 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 upon 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 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 lies in 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 to 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 way of 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 muscles index which does not preferentially assess diaphragm function, while it is also non-invasive and simple to perform. Other methods have been utilised to assess respiratory muscle function such as diaphragmatic electromyography (EMG_{Di})[22] or sniff nasal inspiratory pressure (SNIP).[23] However, surface EMG_{Di} in children would be considerably affected by electrical noise from neighboring muscle groups while nostril occlusion for measurement of SNIP might be poorly tolerated in young children and SNIP values might vary substantively for anatomical 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 of $P_{0.1}$ in our study might reflect developmental changes which are 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 relating to increasing muscle mass and body growth.[28] Values of P_{Imax} have been previously reported in children.[23] Our study reports similar values for maximal respiratory pressures with 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, which given that respiratory muscles are skeletal muscles 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 Ti by a single power function of time, assuming that pressure increases linearly over Ti. 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

Please cite this article in press as: Theodore Dassios, Gabriel Dimitriou, Determinants of inspiratory muscle function in healthy children, Journal of Sport and Health Science (2016), doi: 10.1016/j.jshs.2016.08.002

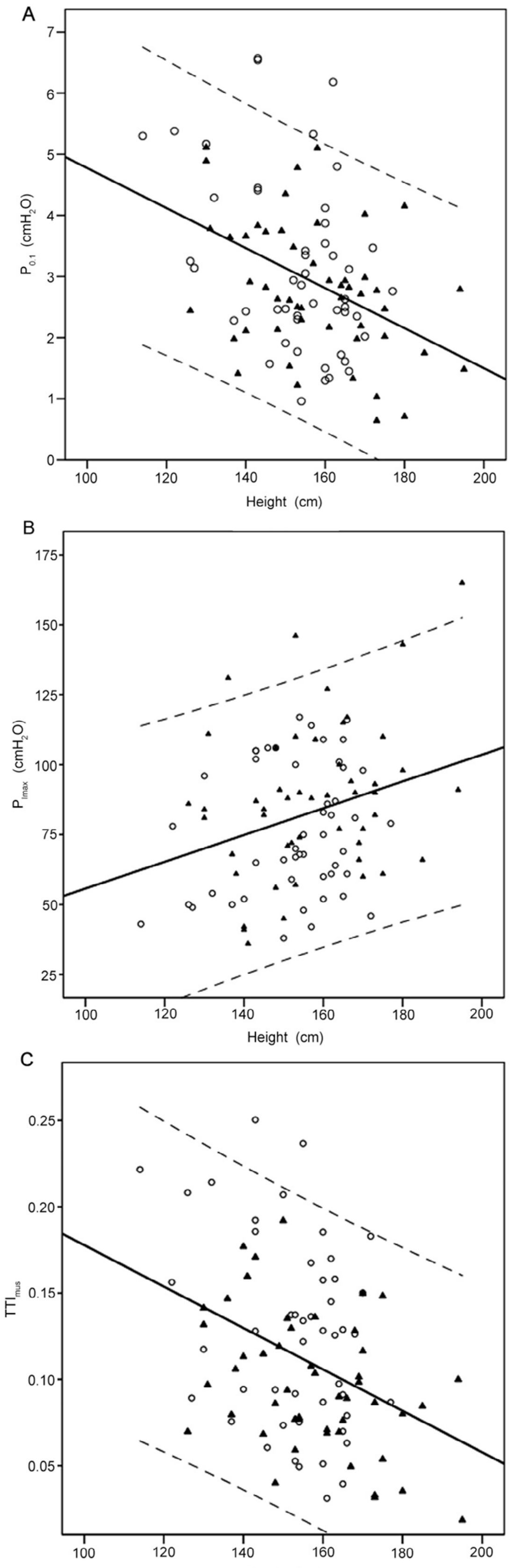

Fig. 1. $P_{0.1}$ (A), P_{Imax} (B), TTI_{mus} (C) and height linear regression analysis. Data for individual subjects, line of regression, and 95% confidence intervals are presented. Male subjects are presented as black triangles and female subjects are presented as white circles.

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

	Standardized coefficient (95%CI)	p value
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; UAMA = upper arm muscle area.

to a specific fatigue threshold of the trans-diaphragmatic 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 were used. Furthermore, our population—however sufficient to describe physiological associations—was relatively modest in size in order to generate predictive equations and did not undergo lung function testing in order 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 for assessing the respiratory muscles and for monitoring respiratory muscle dysfunction and disease progression in children.

Acknowledgment

The statistical guidance of Dr. Richard Parker of the Centre 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 the study, contributed to study design, 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 conflict of interest with relation to this study.

References

1. Dassios T, Katelari A, Doudounakis S, Mantagos S, Dimitriou G. Respiratory muscle function in patients with cystic fibrosis. *Pediatr Pulmonol* 2013;**48**:865-73.
2. Hahn A, Ankermann T, Claass A, Mann M, Lindemann H, Neubauer BA. Non-invasive tension time index in relation to severity of disease in children with cystic fibrosis. *Pediatr Pulmonol* 2008;**43**:973-81.
3. Hayot M, Guillaumont S, Ramonatxo M, Voisin M, Préfaut C. Determinants of the tension-time index of inspiratory muscles in children with cystic fibrosis. *Pediatr Pulmonol* 1997;**23**:336-43.
4. Mulreany LT, Weiner DJ, McDonough JM, Panitch HB, Allen JL. Noninvasive measurement of the tension-time index in children with neuromuscular disease. *J Appl Physiol* 2003;**95**:931-7.
5. Chlif M, Keochkerian D, Mourlhon C, Choquet D, Ahmaidi S. Noninvasive assessment of the tension-time index of inspiratory muscles at rest in obese male subjects. *Int J Obes (Lond)* 2005;**29**:1478-83.
6. Harikumar G, Egberongbe Y, Nadel S, Wheatley E, Moxham J, Greenough A, et al. Tension-time index as a predictor of extubation outcome in ventilated children. *Am J Respir Crit Care Med* 2009;**180**:982-8.
7. Mellies U, Stehling F, Dohna-Schwake C. Normal values for inspiratory muscle function in children. *Physiol Meas* 2014;**35**:1975-81.
8. Dimitriou G, Papakonstantinou D, Stavrou EF, Tzifas S, Vervenioti A, Athanassiadou A, et al. Angiotensin-converting enzyme gene polymorphism and respiratory muscle function in infants. *Pediatr Pulmonol* 2010;**45**:1233-9.
9. Dassios T, Katelari A, Doudounakis S, Dimitriou G. Aerobic exercise and respiratory muscle strength in patients with cystic fibrosis. *Respir Med* 2013;**107**:684-90.
10. Orenstein DM, Franklin BA, Doershuk CF, Hellerstein HK, Germann KJ, Horowitz JG, et al. Exercise conditioning and cardiopulmonary fitness in cystic fibrosis. The effects of a three-month supervised running program. *Chest* 1981;**80**:392-8.
11. American Thoracic Society/European Respiratory Society. ATS/ERS Statement on respiratory muscle testing. *Am J Respir Crit Care Med* 2002;**166**:518-624.
12. Ramonatxo M, Boulard P, Préfaut C. Validation of a noninvasive tension-time index of inspiratory muscles. *J Appl Physiol* 1995;**78**:646-53.
13. Gaultier C. Tension-time index of inspiratory muscles in children. *Pediatr Pulmonol* 1997;**23**:327-9.
14. Black LF, Hyatt RE. Maximal respiratory pressures: normal values and relationship to age and sex. *Am Rev Respir Dis* 1969;**99**:696-702.
15. Kuczmarski RJ, Ogden CL, Guo SS. *2000 CDC growth charts for the United States: methods and development. Vital and health statistics*. Hyattsville, MD: Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics; 2002.
16. Ramsey BW, Farrell PM, Pencharz P. Nutritional assessment and management in cystic fibrosis: a consensus report. The Consensus Committee. *Am J Clin Nutr* 1992;**55**:108-16.
17. Frisancho AR. New norms of upper limb fat and muscle areas for assessment of nutritional status. *Am J Clin Nutr* 1981;**34**:2540-5.
18. Department of Health Physical Activity, Health Improvement and Protection. Start active, stay active: a report on physical activity from the four home countries' chief medical officers. Avialable at: https://www.sportengland.org/media/2928/dh_128210.pdf. [accessed 11.07.2011].
19. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Division of Nutrition, Physical Activity and Obesity. Fact sheet for health professionals on physical activity guidelines for children and adolescents. Avialable at: https://www.cdc.gov/physicalactivity/downloads/pa_fact_sheet_adults.pdf. [accessed 01.12.2015].
20. Dassios T. Determinants of respiratory pump function in patients with cystic fibrosis. *Paediatr Respir Rev* 2015;**16**:75-9.
21. Glenmark B, Nilsson M, Gao H, Gustafsson JA, Dahlman-Wright K, Westerblad H. Difference in skeletal muscle function in males vs. females: role of estrogen receptor-beta. *Am J Physiol Endocrinol Metab* 2004;**287**:E1125-31.
22. Maarsingh EJ, van Eykern LA, Sprikkelman AB, Hoekstra MO, van Aalderen WM. Respiratory muscle activity measured with a noninvasive EMG technique: technical aspects and reproducibility. *J Appl Physiol* 2000;**88**:1955-61.
23. Stefanutti D, Fitting JW. Sniff nasal inspiratory pressure. Reference values in Caucasian children. *Am J Respir Crit Care Med* 1999;**159**:107-11.
24. Bridger GP, Proctor DF. Maximum nasal inspiratory flow and nasal resistance. *Ann Otol Rhinol Laryngol* 1970;**79**:481-8.
25. Younes M, Riddle W, Polacheck J. A model for the relation between respiratory neural and mechanical outputs. III. Validation. *J Appl Physiol Respir Environ Exerc Physiol* 1981;**51**:990-1001.
26. Amin R. Chronic respiratory failure. In: Chernick V, Wilmott R, Bush A, editors. *Kendig's disorders of the respiratory tract in children*. 7th ed. Philadelphia, PA: Saunders Elsevier; 2006.p.243-58.
27. Chernick V, West JB. The functional basis of respiratory disease. In: Chernick V, Wilmott R, Bush A, editors. *Kendig's disorders of the respiratory tract in children*. 7th ed. Philadelphia, PA: Saunders Elsevier; 2006.p.38-9.
28. Scott CB, Nickerson BG, Sargent CW, Platzker AC, Warburton D, Keens TG. Developmental pattern of maximal transdiaphragmatic pressure in infants during crying. *Pediatr Res* 1983;**17**:707-9.
29. Tomalak W, Pogorzelski A, Prusak J. Normal values for maximal static inspiratory and expiratory pressures in healthy children. *Pediatr Pulmonol* 2002;**34**:42-6.
30. Szeinberg A, Marcotte JE, Roizin H, Mindorff C, England S, Tabachnik E, et al. Normal values of maximal inspiratory and expiratory pressures with a portable apparatus in children, adolescents, and young adults. *Pediatr Pulmonol* 1987;**3**:255-8.
31. Smyth RJ, Chapman KR, Rebuck AS. Maximal inspiratory and expiratory pressures in adolescents. Normal values. *Chest* 1984;**86**:568-72.
32. Gaultier C, Zinman R. Maximal static pressures in healthy children. *Respir Physiol* 1983;**51**:45-61.
33. Elliott MW, Mulvey DA, Green M, Moxham J. An evaluation of P0.1 measured in mouth and oesophagus, during carbon dioxide rebreathing in COPD. *Eur Respir J* 1993;**6**:1055-9.

Please cite this article in press as: Theodore Dassios, Gabriel Dimitriou, Determinants of inspiratory muscle function in healthy children, Journal of Sport and Health Science (2016), doi: 10.1016/j.jshs.2016.08.002