Normal values for inspiratory muscle function in children

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Received 25 March 2014, revised 1 August 2014
Accepted for publication 5 August 2014
Published 17 September 2014

Abstract
Assessment of inspiratory muscle function (IMF) is limited in children with neuromuscular disorders, because respiratory muscle tests are poorly standardized and valid normative data are unavailable. We investigated maximum inspiratory pressure after exhalation to residual volume (MIP), mouth occlusion pressure (P0.1) and time of inspiration during quiet breathing and derived inspiratory muscle load (P0.1/MIP), and tension time index (TTI) in 301 healthy schoolchildren 6–16 years old. Gender-specific and age-dependent percentile curves for MIP were drawn with the median, 5%, 10%, 25%, 75% and 95% percentile. P0.1 was equal in boys and girls (0.23 ± 0.11 kPa), while MIP was significantly higher in boys (6.8 ± 2.2 versus 5.8 ± 2.4 kPa). Consequently, P0.1/MIP (4.8% ± 3.2% versus 4.0% ± 3.1%) and TTI (0.2 ± 0.14 versus 0.16 ± 0.14) were significantly higher in girls. MIP was 2.90 + 0.36 × age (kPa) and 3.19 + 0.24 × age (kPa) in boys and girls, respectively. The 95% confidence intervals for boys and girls, respectively, were MIP, 6.3–7.3 kPa and 5.4–6.2 kPa; P0.1/MIP, 3.5%–4.5% and 4.3%–5.3%; TTI, 0.14–0.18 and 0.18–0.22; and P0.1, 0.20–0.24 kPa for both. IMF in children has a wide interindividual variability; however percentile curves facilitate a longitudinal assessment of individual patients. Furthermore, narrow confidence intervals allow for comparisons of study populations, making IMF an appropriate endpoint for clinical trials.

Keywords: inspiratory muscle function, maximum inspiratory pressure, mouth occlusion pressure, work of breathing, tension time index, respiratory muscle weakness

(Some figures may appear in colour only in the online journal)
1. Introduction

Disorders of the respiratory muscles occur in many diseases, and the severity varies widely. Respiratory muscles may be primarily affected in neuromuscular disorders (NMDs) such as Duchenne muscular dystrophy and spinal muscular atrophy (Iandelli et al. 2001, Nicot et al. 2006, Terzi et al. 2008, Fauroux et al. 2009b). Additionally, secondary deterioration has been observed in patients with severe illness (e.g., critical illness myopathy), diseases with involvement of the skeletal system (e.g., scoliosis), and primary lung diseases (e.g., cystic fibrosis) (Mier et al. 1990, Heijerman 1993, Campellone 2007, Inal-Ince et al. 2009).

Weakness of the inspiratory muscles can lead to acute or chronic respiratory failure and thereby contribute to major morbidity in these patients (Rochester and Arora 1983, Fitting 1990, Dubowitz 1995). On the other hand, it has been shown that repetitive training can improve inspiratory muscle strength in both healthy and affected individuals (Koessler et al. 2001, McConnell et al. 2003). Different methods have been developed to assess inspiratory muscle function (IMF) (Decramer and Scano 1994, Mellies et al. 2005). Most of these are based on a maximum voluntary inspiration or sniff via mouth or nose against an occluded airway. The resulting maximum inspiratory pressure (MIP) or sniff inspiratory pressure (Snip) measurements reflect the total inspiratory force with respect to the capacity of the inspiratory muscles. Additionally, it is possible to assess the work of breathing by the following noninvasive tests: (i) P0.1 is the mouth occlusion pressure at 100 ms during quiet breathing and is intended to measure the actual central respiratory drive. (ii) P0.1/MIP is the ratio between the respiratory drive and the capacity of the inspiratory muscles; it represents the inspiratory muscle load. (iii) The tension time index (TTI) is a dimensionless index of the inspiratory muscle force to the inspiration time. These tests to assess inspiratory muscle load and work may be more relevant than the static MIP and Snip tests and have been shown to predict inspiratory failure (Decramer and Scano 1994, Mulreany et al. 2003, Mellies et al. 2005, Fauroux et al. 2009a).

In children, inspiratory muscle strength and muscle strength in general strongly depend on the child’s age. Furthermore, reliable assessments require normative data, which are only available for MIP and Snip pressures (Gaultier and Zinman 1983, Wilson et al. 1984, Stefanutti and Fitting 1999, Tomalak et al. 2002). However, the marked interindividual variability of inspiratory muscle pressures in healthy children makes data interpretation difficult. Values between 40 cm and 100 cm H2O are within the normal range in all subjects. Intraindividual variability is at least 10% (Gaultier and Zinman 1983, American Thoracic Society/European Respiratory Society 2002). The aim of the present study was to expand our knowledge of IMF in children by (i) establishing normative data for MIP, P0.1, P0.1/MIP, and TTI; (ii) calculating confidence intervals to improve comparability of data within and among clinical trials; and (iii) drawing percentile curves to facilitate the assessment of individuals.

2. Methods

2.1. Study population

A total of 332 pupils between 6 and 16 years old who attended a secondary school in an urban area were asked to participate in the study. School authorities were informed about the study protocol, and the parents or caregivers of all children gave their written informed consent. Children with a history, symptoms, or diagnosis of asthma were excluded from participation. Additional exclusion criteria were abnormal spirometry with restrictive (forced vital capacity [FVC] < 80% predicted and forced expiratory volume in 1 s [FEV1]/FVC > 75%), obstructive
2.2. Spirometry and respiratory muscle function

Spirometry (inspiratory VC [IVC], FVC, and FEV1) was performed in upright and supine positions according to American Thoracic Society (ATS) standards, and predicted values were derived from published data (American Thoracic Society/European Respiratory Society 2002). P0.1, MIP, inspiratory time (TI), and respiratory cycle time (TTOT) were measured with a hand-held spirometer/manometer (Zan Meßgeräte, Oberthulba, Germany). MIP was considered to be the highest of three forced maximum inspiratory efforts after slow and complete exhalation to residual volume (RV) with no residual flow. P0.1, TI, and TTOT were averaged from six measures during 1 min of quiet tidal breathing. In accordance with published methods, noninvasive TTI of the respiratory muscles was calculated as TTI = Pi/MIP × TI/TTOT. The mean inspiratory pressure (Pi) was estimated as 5 × P0.1 × Ti (Mulreany et al 2003). Inspiratory muscle load was defined as the ratio of P0.1 to MIP (%).

2.3. Statistics

Statistical analysis was performed with the STATISTICA 6.0 software package. Data are presented as mean and standard deviation and as 95% confidence interval. Comparisons of two independent groups were analyzed by Mann–Whitney U-test. The Pearson coefficient was used to describe univariate correlations between IMF tests and anthropometric data. Multiple regression analysis was performed for each of the inspiratory muscle measures, with gender, age, height, and weight as independent variables. Regression equations for predictive values were calculated. A p value of <0.05 was considered significant. Gender-specific and age-dependent percentile curves for MIP were drawn with the median, 5%, 10%, 25%, 75%, and 95% percentile.

3. Results

A total of 332 schoolchildren participated in the study. Eleven pupils were excluded because of a history of wheezing, and a further 20 were excluded because spirometry indicated bronchial obstruction. Thus, 301 children were included in the data evaluation: 148 girls and 153 boys. There were no significant differences between girls and boys with regard to weight, height, and age. Anthropometric data did not differ from that of normal values for the general population (table 1).

Table 1. Respiratory muscle function in girls and boys.

| Measurements | Girls | Boys | All     |
|--------------|-------|------|---------|
| Age (y)      | 11.0 ± 2.8 (10.6–11.5) | 10.9 ± 2.9 (10.4–11.4) | 11.0 ± 2.9 (10.7–11.3) |
| Weight (kg)  | 40.7 ± 13.9 (38.4 ± 42.9) | 42.7 ± 15.4 (40.2–45.1) | 41.7 ± 14.7 (40.0–43.4) |
| Height (m)   | 1.48 ± 0.16 (1.45–1.51) | 1.50 ± 0.19 (1.48–1.53) | 1.49 ± 0.18 (1.47–1.51) |
| MIP (kPa)    | 5.8 ± 2.4 (5.4–6.2) | 6.8 ± 2.2 (6.3–7.3) * | 6.3 ± 2.9 (6.0–6.7) |
| P0.1 (kPa)   | 0.23 ± 0.11 (0.21–0.25) | 0.22 ± 0.11 (0.20–0.24) | 0.23 ± 0.11 (0.21–0.24) |
| P0.1/MIP (%) | 4.8 ± 3.2 (4.3–5.3) | 4.0 ± 3.1 (3.5–4.5) * | 4.4 ± 3.2 (4.0–4.8) |
| TTI          | 0.198 ± 0.139 (0.18–0.22) | 0.161 ± 0.137 (0.14–0.18) * | 0.179 ± 0.139 (0.16–0.2) |

Mean ± SD and 95% confidence interval (in parentheses).
MIP, maximum inspiratory pressure; TTI, tension time index.
*p < 0.05 for comparisons of mean values between boys and girls.

(FEV1 < 75% and/or FEV1/FVC < 75%), or combined ventilatory defect. Data from 301 children were used for statistical analysis.
Lung function was normal in all children. FVC was 102% ± 8% predicted, and FeV1 was 98% ± 6% predicted. Mean values and 95% confidence intervals for P0.1, MIP, P0.1/MIP, and TTI are provided in Table 1. Mouth occlusion pressures (P0.1) were identical in both genders, and MIPs were significantly higher in boys. Consequently, inspiratory muscle load (P0.1/MIP) and work of breathing (TTI) were significantly higher in girls.

There was wide interindividual variability for the parameters of IMF. The variation coefficients were as follows: Girls, MIP = 0.41; P0.1 = 0.48; P0.1/MIP = 0.67; and TTI = 0.70. Boys, MIP = 0.32; P0.1 = 0.50; P0.1/MIP = 0.78; and TTI = 0.85. Table 2 shows the linear correlations between IMF variables and anthropometric data. All correlations were highly significant: \( p < 0.001 \) for MIP and \( p < 0.0001 \) for P0.1, P0.1/MIP, and TTI.

Multiple regression analysis revealed age (years) was superior to height (cm) in predicting IMF variables. Regression equations for IMF variables were as follows: Girls, MIP = 3.19 + 0.24 \times age (kPa); P0.1 = 0.49 − 0.024 \times age (kPa); TTI = 0.48 − 0.026 \times age; and P0.1/MIP = 0.13 − 0.0074 \times age (%). Boys, MIP = 2.90 + 0.36 \times age (kPa); P0.1 = 0.46 − 0.022 \times age (kPa); TTI = 0.41 − 0.025 \times age; and P0.1/MIP = 0.105 − 0.006 \times age (%).

Age-dependent percentile curves for girls and boys are displayed in Figures 1 and 2(a). Figure 2(b) shows the course of MIP over 4 years in a boy with Duchenne muscular dystrophy.

### Table 2. Univariate linear correlations between respiratory muscle function parameters and anthropometric data.

| Gender | Girls | MIP   | P0.1  | P0.1/MIP | TTI  |
|--------|-------|-------|-------|----------|------|
| Girls  | Age   | 0.276 | −0.612| −0.633   | −0.52|
|        | Weight| 0.32  | −0.58 | −0.60    | −0.47|
|        | Height| 0.30  | −0.48 | −0.52    | −0.41|
|        | Age   | 0.34  | −0.57 | −0.57    | −0.48|
| Boys   | Weight| 0.36  | −0.57 | −0.57    | −0.48|
|        | Height| 0.37  | −0.46 | −0.50    | −0.43|

MIP, maximum inspiratory pressure; P0.1, mouth occlusion pressure; P0.1/MIP, inspiratory muscle load; TTI, tension time index.
In the present study, we used a noninvasive technique to investigate IMF in a large population of healthy children. Our results confirm the high interindividual variability of MIP in healthy subjects and the dependence of MIP on gender and age (Gaultier and Zinman 1983, Wilson et al. 1984, Tomalak et al. 2002). New and important clinical information yielded by our study includes (i) percentile curves that allow for longitudinal assessment of individual patients, (ii) normal values for inspiratory muscle load (P0.1/MIP) and work of breathing (TTI), and (iii) confidence intervals that facilitate the assessment of populations.

Normal IMF values and predictive equations in relatively large samples that include children of all age groups have been reported in only a few studies. Gaultier et al. studied maximum static pressures at different lung volumes in 119 schoolchildren aged 7–13 years and found that MIP at RV was higher than pressures generated at functional residual capacity (Gaultier and Zinman 1983). Wilson et al. studied MIP at RV in 235 children aged 6–17 years (Wilson et al. 1984); we studied MIP in a similar group of 300 healthy children aged 6–17 years. Like Wilson et al., we investigated MIP after exhalation to RV; however, despite a broad consistency between our results and theirs, in our population, the mean values were approximately 10% lower.

In boys, throughout the period of growth, the mean MIP increased from about 5kPa at 6–7 years of age to 9kPa at 16–17 years of age. In girls, the mean MIP increased from about 4.5 to 7.5kPa. However, the marked interindividual variability of inspiratory muscle pressure in healthy children makes data interpretation difficult. Values between 4.0kPa and 15kPa were within the normal range in all subjects. Due to these limitations, the assessment of IMF in individual patients is far more vague than the assessment of lung function by spirometry. Nevertheless, inspiratory muscle testing is a valuable tool for the evaluation of patient groups and populations and for correlations with other respiratory parameters (American Thoracic Society/European Respiratory Society 2002).

There are several clinical indications for the evaluation of IMF, including acute disease and chronic neurological disorders with suspected involvement of the respiratory muscles. Despite difficulties in interpretation, regular measurements of patient MIP can provide additional information regarding the course of inspiratory muscle strength. Repeated measurements are recommended for the documentation of disease progression and recovery.
Observably low MIP (<3 kPa in girls and <4 kPa in boys) is always suggestive of predominant diaphragm weakness and should entail additional VC and MIP measurements in the supine position. In patients with diaphragm weakness, a VC decline of 25% or more in the supine position is accompanied by an MIP decline of 10%–20% (Mier-Jedrzejowicz et al 1988).

Patients with NMDs are at particularly high risk for respiratory complications; in these patients, frequent and early evaluation is crucial, because MIP may decrease before VC. De Troyer et al found that in patients with NMD, VC remains normal until inspiratory muscle strength has fallen below 50% predicted (De Troyer et al 1980). Therefore, clinicians are recommended to obtain and document MIP with every spirometry (American Thoracic Society/European Respiratory Society 2002, Wallgren-Pettersson et al 2004). Considering the results in light of the percentile curves yielded by our study will increase the utility of this measurement. Figure 2(b) illustrates the course of MIP in a boy with Duchenne muscular dystrophy. Although his MIP values were always within the normal range, when these values are considered with respect to the MIP percentile curves for boys, an early and continuous decline in inspiratory muscle strength becomes apparent. The percentile curves were drawn from a small population and therefore should be handled with care. Thus, for example, the peak of the higher MIP percentiles at ages 11–13 years is not reasonable and is likely due to the limited number of subjects included into the analysis. Therefore we recommend using the percentile curves exclusively for documentation of the MIP in individual subjects and with a focus on the chronological course and the lower limit of normal. However, documentation of individual MIPs in a percentile curve may be useful during longer treatments, interventions, and studies in which there is a potential impact on inspiratory muscle strength. Examples include steroid treatment, inspiratory muscle training, and upcoming clinical trials that address neuromuscular disorders (Arnett et al 2009, Garralda et al 2013, Kissel et al 2014).

To the best of our knowledge, this is the first study to report normal values for P0.1/MIP and TTI in healthy children. Both measures are suitable for noninvasive assessments of inspiratory muscle load and work of breathing (Decramer and Scano 1994, Mellies et al 2005, Fauroux et al 2009a). Mulreany et al (2003) showed that the TTI was higher in 41 patients with NMDs than in controls. Additionally, TTI increases with disease progression in boys with Duchenne muscular dystrophy (Hahn et al 2009) and decreases after use of noninvasive ventilation as a measure of inspiratory muscle unloading (Koessler et al 2001). Ragette et al (2002) demonstrated that inspiratory muscle load is inversely correlated with VC and with the occurrence of sleep-related breathing disorders in patients with NMD. However, a methodical limitation of this study is that P0.1 and MIP were measured at different lung volumes, P0.1 at FRC and MIP at RV.

The result from our study that will probably be of greatest benefit to researchers is the narrow confidence intervals of the IMF tests, which will allow for comparisons of study populations. Thus, IMF may now be an appropriate endpoint for clinical trials.

In summary, the results of the present study partially ameliorate the previous lack of data regarding inspiratory muscle testing in children. They should facilitate assessments not only of individual patients, but also of populations.

References

Arnett A L, Chamberlain J R and Chamberlain J S 2009 Therapy for neuromuscular disorders Curr. Opin. Genet. Dev. 19 290–7

American Thoracic Society/European Respiratory Society 2002 ATS/ERS statement on respiratory muscle testing Am. J. Respir. Crit. Care Med. 166 518–624

Decramer M and Scano G 1994 Assessment of respiratory muscle function Eur. Respir. J. 7 1744–5
De Troyer A, Borenstein S and Cordier R 1980 Analysis of lung volume restriction in patients with respiratory muscle weakness *Thorax* **35** 603

Dubowitz V 1995 *Muscle Disorders in Childhood* (London: W B Saunders)

Fauroux B, Aubertin G, Clement A, Lofaso F and Bonora M 2009 Which tests may predict the need for noninvasive ventilation in children with neuromuscular disease? *Respir. Med.* **103** 574–81

Fauroux B, Aubertin G, Cohen E, Clement A and Lofaso F 2009b Sniff nasal inspiratory pressure in children with muscular, chest wall or lung disease *Eur. Respir. J.* **33** 113–7

Fitting J W 1990 Muscle fatigue in acute respiratory failure *Lung* **168** 823–8

Garralda M E, McConachie H, Le Couteur A, Sriranjan S, Chakrabarti I, Cirak S, Guglieri M, Bushby K and Muntoni F 2013 Emotional impact of genetic trials in progressive paediatric disorders: a doseranging exon-skipping trial in Duchenne muscular dystrophy *Child: Care Health Dev.* **39** 449–55

Gaultier C and Zinman R 1983 Maximal static pressures in healthy children *Respir. Physiol.* **51** 45

Hahn A, Duisberg B, Neubauer B A, Stephani U and Rideau Y 2009 Noninvasive determination of the tension-time index in Duchenne muscular dystrophy *Am. J. Phys. Med. Rehabil./Assoc. Acad. Physiatr.* **88** 322–7

Heijerman H G 1993 Chronic obstructive lung disease and respiratory muscle function: the role of nutrition and exercise training in cystic fibrosis *Respir. Med.* **87** 49–51

Iandelli I, Gorini M, Misuri G, Gigliotti F, Rosi E, Duranti R and Scano G 2001 Assessing inspiratory muscle strength in patients with neurologic and neuromuscular diseases: comparative evaluation of two noninvasive techniques *Chest* **119** 1108–113

Inal-Ince D, Savci S, Arikian H, Sigamal M, Vardar-Yagli N, Nsobnak-Guclu M and Dogru D 2009 Effects of scoliosis on respiratory muscle strength in patients with neuromuscular disorders *Spine J.: Official J. North Am. Spine Soc.* **9** 981–6

Kissel J T et al 2014 Project cure spinal muscular atrophy investigators N. SMA valiant trial: a prospective, double-blind, placebo-controlled trial of valproic acid in ambulatory adults with spinal muscular atrophy *Muscle Nerve* **49** 187–92

Koessler W, Wanke T, Winkler G, Nader A, Toifl K, Kurz H and Zwick H 2001 2 years experience with inspiratory muscle training in patients with neuromuscular disorders *Chest* **120** 765

McConnell T R, Mandak J S, Sykes J S, Fesniak H and Dasgupta H 2003 Exercise training for heart failure patients improves respiratory muscle endurance, exercise tolerance, breathlessness, and quality of life *J. Cardiopulm. Rehabil.* **23** 10–16

Mellies U, Dohna-Schwake C and Voit T 2005 Respiratory function assessment and intervention in neuromuscular disorders *Curr. Opin. Neurol.* **18** 543–7

Mier A, Redington A, Brophy C, Hodson M and Green M 1990 Respiratory muscle function in cystic fibrosis *Thorax* **45** 750–2

Mier-Jedrzejowicz A, Brophy C, Moxham J and Green M 1988 Assessment of diaphragm weakness *Am. Rev. Respir. Dis.* **137** 877–83

Mulreany L T, Weiner D J, McDonough J M, Panitch H B and Allen J L 2003 Noninvasive measurement of the tension-time index in children with neuromuscular disease *J. Appl. Physiol.* **95** 931–7

Nicot F, Hart N, Forin V, Boule M, Clement A, Polkey M I, Lofaso F and Fauroux B 2006 Respiratory muscle testing: a valuable tool for children with neuromuscular disorders *Am. J. Respir. Crit. Care Med.* **174** 67–74

Ragette R, Mellies U, Schwake C, Voit T and Teschler H 2002 Patterns and predictors of sleep disordered breathing in primary myopathies *Thorax* **57** 724–8

Rochester D F and Arora N S 1983 *Respiratory muscle failure Med. Clin. North Am.* **67** 573–97

Stefanutti D and Fitting J W 1999 Sniff nasal inspiratory pressure. Reference values in Caucasian children *Am. J. Respir. Crit. Care Med.* **159** 107–11

Terzi N, Orlikowski D, Ferziman C, Lejaile M, Falaize L, Louis A, Raphael J C, Fauroux B and Lofaso F 2008 Measuring inspiratory muscle strength in neuromuscular disease: one test or two? *Eur. Respir. J.* **31** 93–8

Tomala K, Pogorzelski A and Prusak J 2002 Normal values for maximal static inspiratory and expiratory pressures in healthy children *Pediatr. Pulmonol.* **34** 42–6

Wallgren-Pettersson C, Bushby K, Mellies U and Simonds A 2004 117th ENMC Workshop: Ventilatory Support in Congenital Neuromuscular Disorders—Congenital Myopathies, Congenital Muscular Dystrophies, Congenital Myotonic Dystrophy and SMA (II) (4–6 April 2003, Naarden, The Netherlands). *Neuromuscul. Disord.* **14** 56–69

Wilson S H, Cooke N T, Edwards R H and Spiro S G 1984 Predicted normal values for maximal respiratory pressures in caucasian adults and children *Thorax* **39** 535

1981