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REVIEW

Ventilatory muscle strength in cystic fibrosis patients: a literature review

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ABSTRACT: ***Ventilatory muscle strength in cystic fibrosis patients: a literature review. J.P. Heinzmann-Filho, P.J.C. Cauduro Marostica, M.V.F. Donadio.***

The ventilatory mechanic changes that occur in cystic fibrosis (CF) patients may lead to alterations in the respiratory muscle strength levels. However, the findings regarding the strength profile in these patients are still contradictory.

Objective: To evaluate, trough a literature review, the respiratory muscle strength behavior in CF patients.

We have performed a search in Medline/Pubmed, Scielo, IBECS and LILACS databases selecting observational cross-sectional, prospective or retrospective studies, as well as randomized clinical trials, published between 1981 and 2011, using the following terms: cystic fibrosis, respiratory muscle strength, inspiratory maximal pressure and muscle training.

The majority of the studies 71,24% have shown normal or above normal respiratory muscle strength, whilst 28,57% demonstrated reduced or near-normal values. Most of these findings were attributed to an increased work of breathing as a result of airway obstruction and chronic persistent cough.

Taken together, the analyses of selected studies have showed conflicting findings regarding respiratory muscle strength behavior in these patients. However, most of the studies seem to indicate that CF patients presented maximum respiratory pressures normal or above predicted values.

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Keywords: Cystic fibrosis, Muscle strength, Muscle training.

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Introduction

Cystic fibrosis (CF) is a genetic disease characterized by recessive autosomal transmission resulting from alterations in the CF transmembrane regulator gene located in chromosome 7 [1, 2]. These mutations cause a complex dysfunction of organs including the digestive, metabolic, reproductive and respiratory systems because the transport of ions and water in the epithelial cells becomes compromised [3]. The respiratory dysfunction appears to be the main aggravating factor, since it is the greatest cause of mortality in this population [2] This alteration leads to different degrees of clinical manifestations with modifications in the levels of pulmonary function, presenting chronic suppurative lung disease with destruction of the pulmonary parenchyma [1]. Air trapping, pulmonary hyperinsuflation and increased airway resistance may also occur, with increasing involvement of the respiratory system, altering the thoraco-abdominal balance [1, 4].

Some studies demonstrate that hyperinsuflation combined with malnutrition, could be a predisposing factor for the development of respiratory muscle weakness and, once it is installed, increased muscle fatigue and dyspnea. In association with lack of use, hypoxemia, acidosis and electrolytic disorders may even further favor the reduction of respiratory muscle strength [5, 6]. On the other hand, chronic cough and increased ventilatory effort appear to favor increased muscle strength [4, 6]. These changes alter the chest shape, placing inspiratory muscles at a disadvantage, especially the diaphragm, diminishing the respiratory compliance, increasing energy expenditure and oxygen consumption for breathing [7]. Based on these muscle modifications, it is essential to measure the respiratory muscle strength levels by manovacuometry [1]. This method is simple and non invasive, allowing the quantification of the inspiratory and expiratory muscle function [8, 9].

Despite the relevance of the topic and the frequent use of this method to evaluate and follow patients with CF, there does not yet appear to be a consensus regarding the results expected for respiratory muscle strength in these patients, ranging from the reduction of muscle strength levels to in-

creased strength [5, 10, 11]. This can probably be attributed to the methodological differences employed, different age groups, measuring instruments, nutritional states and distinct degrees of lung involvement [5, 6]. Thus, considering the controversial evidence about alterations of respiratory muscle strength in this population and the importance of persistent respiratory modifications present in these patients, the purpose of this study was to evaluate, trough a literature review, the behavior of respiratory muscle strength in CF patients. The compilation and analysis of the available data may help the professionals in the CF multidisciplinary team to better understand, evaluate and treat respiratory muscle strength related disorders.

Methods

The study consists of a literature review performed by researching the Medline/Pubmed, Scielo, IBECS and LILACS data bases. Cross-sectional, prospective or retrospective observational studies, as well as randomized clinical trials were selected, that had been published during the period from 1981 to 2011, in English, where the keywords were present in the title or in the abstract. The key words used were: *cystic fibrosis*, *respiratory muscle strength*, *inspiratory maximal pressure* and *muscle training*.

The inclusion criteria used were studies that evaluated the respiratory muscle strength in clinically stable patients with a confirmed diagnosis of cystic fibrosis, who expressed respiratory muscle strength values as a percentage of the predicted, Z-score or compared with a control group (healthy individuals). The studies that reported respiratory muscle strength in water centimeters (cmH_2O), but presented the findings as compared with normality values were also included. Respiratory muscle strength was considered normal, below or above normality according to the classification by the authors themselves. In the absence of a classification, the results were analyzed and called normal or increased when most individuals had values above 80% of the predicted value. On the other hand, review studies, other measuring techniques that haven't used a manovacuometer, articles that did not evaluate respiratory strength and studies that only used respiratory muscle strength as an outcome for some type of therapeutic intervention without normalizing the data were excluded.

After selecting the articles, they were read using an instrument to systematize the analysis of methods and the main results of the studies. In this way the relevant aspects of each article were selected and written in table form to make a critical and systematic analysis of the evaluations and results contained in them.

Results

Joining the terms *cystic fibrosis* and *respiratory muscle strength*, 47 (forty-seven) articles were found, 22 (twenty-two) of which were selected. Using the terms *cystic fibrosis* and *inspiratory maximal pressure*, 27 (twenty-seven) articles were found, of which 5 (five) were selected. In the last search, using the terms *cystic fibrosis* and *muscle training*, only 1 (one) study was selected. Figure 1 shows the systematization of the article search.

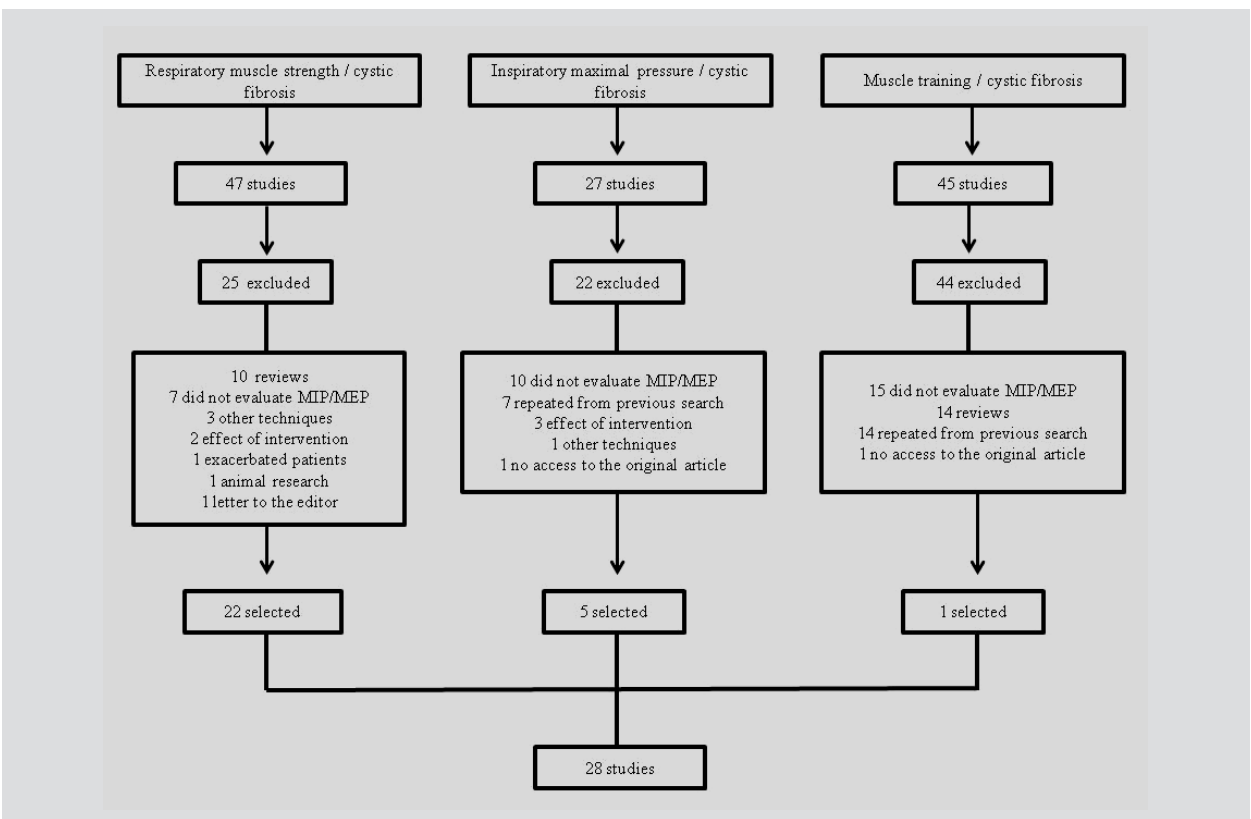

Fig. 1. - Systematization of the search and selection of studies.

Analysis of the studies that evaluated respiratory muscle strength in CF patients showed that the values of maximal inspiratory and expiratory pressures may be normal, increased or decreased. Most studies, 20 articles (71.24%) showed normal or above normal respiratory muscle strength values, while 8 (28.57%) of the studies indicated decreased or close to normal values. The summary of the selected studies is shown in table 1.

Discussion

The findings of normal or above normal respiratory muscle strength are often attributed to increased ventilatory work [5], due to airway obstruction [4, 10, 12] and persistent chronic cough [6], which is common as the disease progresses in CF patients. On the other hand, studies that report decreased respiratory muscle strength generally relate it to several factors including: pulmonary hyperinsuflation [13], alterations in the diaphragm mechanics [14], malnutrition [7], severity of pulmonary disease [15, 16], advanced chronological age [17, 18], and lack of use [5]. In general, the association of these factors may contribute to the development of muscle fatigue, making it easier for dyspnea to occur, increasing energy consumption and the onset of a state of respiratory failure.

When we performed an analysis separating the articles selected according to age group of the sample studied, 7 (25%) evaluated respiratory muscle strength in children and adolescents up to the age of 18 years. Four (57.14%) of these showed reduced strength or close to normal [19-22], and 3 (42.85%) had normal or increased values [18, 23, 24]. On the other hand, when we analyzed the studies in adults (from 18 years of age), there was again a predominance of normal respiratory muscle strength, and 9 (90%) out of a total of 10 studies showed normal or above normal values [5-7, 12, 25-29] while only 1 (10%) reported decreased values [30]. The other studies (39.28%) were not included in the analysis by age group because they did not analyze individuals of different ages separately, showing children and adults together [1, 4, 11, 13, 15-17, 24, 31-33]. This separate analysis of data according to age group appears to indicate that the age factor is not the main aspect related to decreased respiratory muscle strength, considering that reduction of the latter appear to be more closely related to the pediatric age group. This may be due to diminished capacity to perform the maneuvers among the children, which could underestimate the respiratory pressure values and, consequently, determine a reduction in the levels of respiratory muscle strength measured. Another point that should be analyzed is the use of possibly inappropriate reference values, since the fact that equations from other places are often being used, may influence the outcomes of respiratory muscle strength. In a review of standards performed in 1991, the *American Thoracic Society* (ATS) recommends generating reference values of spirometric parameters for each region or site, in order to demonstrate the reality of each population [34]. Thus, it is possible that the respiratory muscle strength values could also be influenced by these population differences, including ethnic and structural aspects that could be distinct and influence the normalization of results. Besides, pulmonary hyperinsuflation is still pointed out by different authors, as one of the main factors related to the reduction of respiratory muscle strength [16, 17]. Studies on normal individuals report that the aging process is associated with a reduction of accessory muscle and diaphragm trophism, and that the age factor can contribute to the decline of maximal static respiratory pressures [9, 35]. However, this does not appear to occur in CF individuals, in whom the factors discussed above and the possibility of self muscle training as a consequence of the pulmonary alterations appears to exert a greater effect on the respiratory muscle strength than aging itself.

Besides these differences and the difficult discernment of the factors that could interfere in the respiratory muscle strength levels, other aspects could also help explain the contradictory findings, such as: the different methodologies used, differences in the subjects' ages, level of pulmonary compromise and variability during maneuvers [5, 13, 14, 36]. Several studies reported that subject variability may be around 7-10%, and that these alterations could be related to the different verbal, motivational stimuli, both by the technician and by the patient himself, the number of evaluators and the differences in the measuring techniques [8, 36-38]. There is also great variability in the number of maneuvers performed in the studies, ranging from a minimum of three maneuvers to a maximum of ten repetitions [1, 6, 13, 16, 30, 31]. However, it is known that the more repetitions are performed, the greater will be the effects of learning and the higher the values that can be obtained, justifying the recommendation that measurements be performed in up to five maneuvers [39]. These factors, when associated with a small sample size, may make it difficult to perform a more homogeneous comparison, and often modify the results of maximal static respiratory pressures.

In summary, analysis of the studies selected showed diverging findings in relation to the behavior of respiratory muscle strength in patients with CF. However, most studies appear to indicate that the individuals with CF studied presented normal or above expected maximal respiratory pressure values. These findings were mostly attributed to increased work and ventilatory demand, especially as a consequence of the chronic obstructive disease and persistent cough. Although there is evidence regarding factors that could modify the outcomes of respiratory muscle strength, the mechanisms that influence their behavior have not yet been fully explained. Factors such as age, compromised pulmonary function and hyperinflation still need further study in this population. Likewise, studies that evaluate not only muscle strength but also a more global view of the respiratory muscle function, including aspects of endurance, for instance, are still needed.

Table 1. - Summary of the selected studies trough the research strategies used

Authors	Year	Country	Population	Age Group	N	Data presentation	Main results
Leroy S *et al*	2011	France	CF	32±12.6 (20-67)	18	% predict	↓ MIP
Dunnink *et al*	2009	Netherlands	CF	26±7 (18-40)	27	% predict	↑ MIP ↔ MEP
Dufresne V *et al*	2009	Belgium	CF Healthy	29.1±6.6 30.2±6.1	38 24	cmH_2O	↑ MIP
Troosters T *et al*	2009	Belgium	CF Healthy	26±8 25±5	64 20	% predict	↔ MIP ↔ MEP
Barry PJ *et al*	2008	Ireland	CF	23.9 (19-40)	15	% predict	↔ MIP ↔ MEP
Hahn A *et al*	2008	Germany Healthy	CF	14 (9-26) 14.5 (9-26)	47 47	% predict	↔ MIP
Ziegler B *et al*	2008	Brazil	CF	23,7±6,4 (16-47)	39	% predict	↔ MIP or ↓ ↔ MEP or ↓
Enright S *et al*	2007	United Kingdom	CF Healthy	22,4 (18-32) 21,7 (18-33)	40 30	cmH_2O	↔ MIP
Zanchet RC *et al*	2006	Brazil	CF	10±5,6 (7-28)	29	cmH_2O	↑ MIP ↑ MEP
Cunha *et al*	2006	Brazil	CF	11±1,9 (8-14)	16	cmH_2O	↔ MIP or ↓ ↔ MEP or ↓
Keochkerian D *et al*	2005	France	CF Healthy	13.1±1.5 (10-14) 13.3±0.5 (11-14)	8 8	cmH_2O	↓ MIP
Barry SC *et al*	2003	Ireland	CF	23.3±5.1 (18-39)	23	% predict	↔ MIP ↔ MEP
de Jong W *et al*	2001	Netherlands	CF Control CF Intervention	19±5,5 (10-25) 17±5,2 (10-25)	8 8	% predict	↑ MIP
Milross MA *et al*	2001	Australia	CF	27±8 (18-49)	30	% predict	↔ MIP or ↑ ↔ MEP
Bradley S *et al*	1999	Australia	CF Healthy	25.9±3.5 27.6±3.2	14 8	cmH_2O	↔ MIP ↔ MEP
Fauroux B *et al*	1999	France	CF	13±4 (6-18)	16	cmH_2O	↓ MIP ↔ MEP
Ionescu AA *et al*	1998	United Kingdom	CF	22,9±3,8	25	cmH_2O	↔ MIP
Alisson JA *et al*	1997	Australia	CF Healthy	26±7,7 (17-44) 24,6±2,4 (21-30)	24 10	% predict	↔ MIP ↔ MEP
Hayot M *et al*	1997	France	CF Healthy	11±2 11±2	16 10	% predict	↔ MIP
Hanning RM *et al*	1993	Canada	CF Control CF Intervention	9,5±2,9 (7-15) 10,6±2,5 (7-15)	7 9	% predict	↔ MIP or ↑ ↔ MEP
Lands LC *et al*	1993	Canada	CF Healthy	21.0±8.38 26.8±8.70	14 16	cmH_2O	↔ MIP or ↑ ↔ MEP
Sawyer EH *et al*	1993	United States	CF Control CF Intervention	9,76±2,57 (7-14) 11,46±2,45 (7-14)	10 10	% predict	↔ MIP or ↑
Mier A *et al*	1990	United Kingdom	CF	21 (16-28)	25	% predict	↔ MIP or ↓ ↔ MEP or ↓
Lands L *et al*	1990	Canada	Control Female Control Anorexia Nervosa Asthma CF	14,6±2 (12-35) 14,3±0,7 (12-35) 14,7±1,9 (12-35) 15,2±1,5 (12-35) 17,8±5,6 (12-35)	14 8 9 10 22	% predict	↔ MIP
Marks J *et al*	1986	Canada	Asthma CF Healthy	12,8±5 (5-25) 14,5±5 (7-23) (7-24)	29 25 80	cmH_2O	↔ MIP ↔ MEP
Szeinberg A *et al*	1985	Canada	CF Healthy	22,1±3,7 (16-35) 22,5±6,8 (17-39)	23 33	cmH_2O	↓ MIP ↓ MEP
Mansell L A *et al*	1984	United States	CF	13,6 (10-17)	11	cmH_2O	↓ MIP ↓ MEP
O'Neill S *et al*	1983	Canada	CF Healthy	14,5±5 (7-23) (7-24)	25 80	cmH_2O	↔ MIP or ↑ ↔ MEP or ↑

CF: cystic fibrosis; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; ↑: increased; ↓: decreased; ↔: normal; N: number of subjects. Age group is presented by mean ± standard deviation (minimum and maximum).

References

1. Zanchet RC, Chagas AM, Melo JS, Watanabe PY, Simões-Barbosa A, Feijo G. Influence of the technique of re-educating thoracic and abdominal muscles on respiratory muscle strength in patients with cystic fibrosis. *J Bras Pneumol* 2006; 32: 123-9.
2. Fiates GMR, Barbosa E, Auler F, Feiten SF, Miranda F. Nutritional Status anda Food intake of Individuals with cytic fibrosis. *Revista de Nutrição* 2001; 14: 95-101.
3. Sahlberg ME, Svantesson U, Thomas EM, Strandvik B. Muscular strength and function in patients with cystic fibrosis. *Chest* 2005; 127: 1587-92.
4. de Jong W, van Aalderen WM, Kraan J, Koëter GH, van der Schans CP. Inspiratory muscle training in patients with cystic fibrosis. *Respir Med* 2001; 95: 31-6.
5. Barry SC, Gallagher CG. Corticosteroids and skeletal muscle function in cystic fibrosis. *J Appl Physiol* 2003; 95: 1379-84.
6. Dunnink MA, Doeleman WR, Trappenburg JC, de Vries WR. Respiratory muscle strength in stable adolescent and adult patients with cystic fibrosis. *J Cyst Fibros* 2009; 8: 31-6.
7. Ionescu AA, Chatham K, Davies CA, Nixon LS, Enright S, Shale DJ. Inspiratory muscle function and body composition in cystic fibrosis. *Am J Respir Crit Care Med* 1998; 158: 1271-6.
8. Wilson SH, Cooke NT, Edwards RH, Spiro SG. Predicted normal values for maximal respiratory pressures in caucasian adults and children. *Thorax* 1984; 39: 535-8.
9. Neder JA, Andreoni S, Lerario MC, Nery LE. Reference values for lung function tests. II. Maximal respiratory pressures and voluntary ventilation. *Braz J Med Biol Res* 1999; 32: 719-27.
10. Lands LC, Heigenhauser GJ, Jones NL. Respiratory and peripheral muscle function in cystic fibrosis. *Am Rev Respir Dis* 1993; 147: 865-9.
11. Mier A, Redington A, Brophy C, Hodson M, Green M. Respiratory muscle function in cystic fibrosis. *Thorax* 1990; 45: 750-2.
12. Enright S, Chatham K, Ionescu AA, Unnithan VB, Shale DJ. The influence of body composition on respiratory muscle, lung function and diaphragm thickness in adults with cystic fibrosis. *J Cyst Fibros* 2007; 6: 384-90.
13. Ziegler B, Lukrafka JL, de Oliveira Abraão CL, Rovedder PM, Dalcin PeT. Relationship between nutritional status and maximum inspiratory and expiratory pressures in cystic fibrosis. *Respir Care* 2008; 53: 442-9.
14. Pinet C, Cassart M, Scillia P, *et al*. Function and bulk of respiratory and limb muscles in patients with cystic fibrosis. *Am J Respir Crit Care Med* 2003; 168: 989-94.
15. 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.
16. Szeinberg A, England S, Mindorff C, Fraser IM, Levison H. Maximal inspiratory and expiratory pressures are reduced in hyperinflated, malnourished, young adult male patients with cystic fibrosis. *Am Rev Respir Dis* 1985; 132: 766-9.
17. Lands L, Desmond KJ, Demizio D, Pavilanis A, Coates AL. The effects of nutritional status and hyperinflation on respiratory muscle strength in children and young adults. *Am Rev Respir Dis* 1990; 141: 1506-9.
18. Sawyer EH, Clanton TL. Improved pulmonary function and exercise tolerance with inspiratory muscle conditioning in children with cystic fibrosis. *Chest* 1993; 104: 1490-7.
19. Cunha MT, Rozov T, de Oliveira RC, Jardim JR. Six-minute walk test in children and adolescents with cystic fibrosis. *Pediatr Pulmonol* 2006; 41: 618-22.
20. Keochkerian D, Chlif M, Delanaud S, Gauthier R, Maingourd Y, Ahmaidi S. Timing and driving components of the breathing strategy in children with cystic fibrosis during exercise. *Pediatr Pulmonol* 2005; 40: 449-56.
21. Fauroux B, Boulé M, Lofaso F, *et al*. Chest physiotherapy in cystic fibrosis: improved tolerance with nasal pressure support ventilation. *Pediatrics* 1999; 103: E32.
22. Mansell AL, Andersen JC, Muttart CR, *et al*. Short-term pulmonary effects of total parenteral nutrition in children with cystic fibrosis. *J Pediatr* 1984; 104: 700-5.
23. 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.
24. Hanning RM, Blimkie CJ, Bar-Or O, Lands LC, Moss LA, Wilson WM. Relationships among nutritional status and skeletal and respiratory muscle function in cystic fibrosis: does early dietary supplementation make a difference? *Am J Clin Nutr* 1993; 57: 580-7.
25. Dufresne V, Knoop C, Van Muylem A, *et al*. Effect of systemic inflammation on inspiratory and limb muscle strength and bulk in cystic fibrosis. *Am J Respir Crit Care Med* 2009; 180: 153-8.
26. Troosters T, Langer D, Vrijsen B, *et al*. Skeletal muscle weakness, exercise tolerance and physical activity in adults with cystic fibrosis. *Eur Respir J* 2009; 33: 99-106.
27. Bradley S, Solin P, Wilson J, Johns D, Walters EH, Naughton MT. Hypoxemia and hypercapnia during exercise and sleep in patients with cystic fibrosis. *Chest* 1999; 116: 647-54.
28. Barry PJ, Waterhouse DF, Reilly CM, McKenna TJ, McKone EF, Gallagher CG. Androgens, exercise capacity, and muscle function in cystic fibrosis. *Chest* 2008; 134: 1258-64.
29. Milross MA, Piper AJ, Norman M, *et al*. Predicting sleep-disordered breathing in patients with cystic fibrosis. *Chest* 2001; 120: 1239-45.
30. Leroy S, Perez T, Neviere R, Aguilaniu B, Wallaert B. Determinants of dyspnea and alveolar hypoventilation during exercise in cystic fibrosis: impact of inspiratory muscle endurance. *J Cyst Fibros* 2011; 10: 159-65.
31. Alison JA, Regnis JA, Donnelly PM, Adams RD, Sutton JR, Bye PT. Evaluation of supported upper limb exercise capacity in patients with cystic fibrosis. *Am J Respir Crit Care Med* 1997; 156: 1541-8.
32. Marks J, Pasterkamp H, Tal A, Leahy F. Relationship between respiratory muscle strength, nutritional status, and lung volume in cystic fibrosis and asthma. *Am Rev Respir Dis* 1986; 133: 414-7.
33. O'Neill S, Leahy F, Pasterkamp H, Tal A. The effects of chronic hyperinflation, nutritional status, and posture on respiratory muscle strength in cystic fibrosis. *Am Rev Respir Dis* 1983; 128: 1051-4.
34. Lung function testing: selection of reference values and interpretative strategies. American Thoracic Society. *Am Rev Respir Dis* 1991; 144: 1202-18.
35. Enright PL, Kronmal RA, Manolio TA, Schenker MB, Hyatt RE. Respiratory muscle strength in the elderly. Correlates and reference values. Cardiovascular Health Study Research Group. *Am J Respir Crit Care Med* 1994; 149 (2 Pt 1): 430-8.
36. Hautmann H, Hefele S, Schotten K, Huber RM. Maximal inspiratory mouth pressures (PIMAX) in healthy subjects - what is the lower limit of normal? *Respir Med* 2000; 94: 689-93.
37. McElvaney G, Blackie S, Morrison NJ, Wilcox PG, Fairbarn MS, Pardy RL. Maximal static respiratory pressures in the normal elderly. *Am Rev Respir Dis* 1989; 139: 277-81.
38. Leech JA, Ghezzo H, Stevens D, Becklake MR. Respiratory pressures and function in young adults. *Am Rev Respir Dis* 1983; 128: 17-23.
39. Souza R. Diretrizes para testes de função pulmonar. *Jornal Brasileiro de Pneumologia* 2002; 28: 155-65.