Late-onset Pompe disease (LOPD): may axial myopathy influence respiratory dysfunction?

annalisa carlucci
  Maugeri Clinical Research Institutes IRCCS Pavia: Istituti Clinici Scientifici Maugeri SpA IRCCS Pavia
nicola Barbarito
  Don Gnocchi Foundation: Fondazione Don Carlo Gnocchi Onlus
alberto malovini
  Maugeri Clinical Research Institutes IRCCS Pavia: Istituti Clinici Scientifici Maugeri SpA IRCCS Pavia
piero ceriana
  Maugeri Clinical Research Institutes IRCCS Pavia: Istituti Clinici Scientifici Maugeri SpA IRCCS Pavia
serena cirio
  Maugeri Clinical Research Institutes IRCCS Pavia: Istituti Clinici Scientifici Maugeri SpA IRCCS Pavia
manuela piran
  Maugeri Clinical Research Institutes IRCCS Pavia: Istituti Clinici Scientifici Maugeri SpA IRCCS Pavia
anna pichiecchio
  Fondazione Istituto Neurologico Nazionale C Mondino Istituto di Ricovero e Cura a Carattere Scientifico
paola de filippi
  University of Pavia: Universita degli Studi di Pavia
cesare danesino
  University of Pavia: Universita degli Studi di Pavia
sabrina ravaglia (✉ sabrina.ravaglia@mondino.it)
  Fondazione Istituto Neurologico Nazionale C Mondino Istituto di Ricovero e Cura a Carattere Scientifico
  https://orcid.org/0000-0001-8749-3706

Abstract

Background

Respiratory dysfunction in Late Onset Pompe Disease (LOPD) is attributed primarily to diaphragm weakness; it is not always proportional to skeletal muscle weakness. Beyond diaphragm and rib cage muscles, we know that posterior trunk muscles participate to inspiration, and abdominal wall muscles contribute to forced expiration. We aimed to investigate whether the involvement of axial muscles detected by muscle MRI may correlate with respiratory dysfunction or influence respiratory functional tests.

Methods

In 19 patients with LOPD in different stages of disease, we analyzed trunk muscle MRI and upright forced vital capacity FVC, postural drop in VC, and maximal inspiratory and expiratory pressures (MIP, MEP).

Results

While upright FVC did not correlate with trunk muscle involvement, postural drop in VC, reflecting diaphragm weakness, was strongly influenced by the severity of involvement of all posterior and anterior muscles.

Conclusion

Trunk muscles involvement in LOPD may reveal respiratory dysfunction and contribute to postural drop in VC. It is likely that axial muscle weakness may impair the compensatory mechanisms occurring in clinostatism, and mainly operated by the abdominal muscles. Detection of axial muscle damage by MRI may thus suggest the need of more extensive respiratory assessment, i.e. by polysomnography, even when upright VC is still within normal ranges.

Introduction

Late-onset Pompe disease (LOPD) (OMIM #232300) is an autosomal recessive myopathy caused by acid alpha–glucosidase (GAA) deficiency. The adult phenotype is a progressive proximal myopathy involving respiratory muscles [1], with the diaphragm showing the most severe involvement [2, 3].

The assessment of respiratory function in LOPD, as well as in other neuromuscular diseases, relies on measurement of forced vital capacity (FVC), postural drop in VC, Maximal Inspiratory/Expiratory Pressures (MIP and MEP). Both postural drop in VC > 20% moving from sitting to supine position [4], and reduced MIP [5], reflects diaphragm weakness.

Diaphragm weakness is the main life-threatening complication in LOPD. Since this complication is not always related to the degree of skeletal muscle weakness [6, 7], it is important to search for respiratory dysfunction independent of the concomitance of motor dysfunction. The reasons for this discrepancy between motor and respiratory dysfunction are unknown: speculations include the possible contribution of anterior horn spinal motor-neurons to diaphragmatic weakness [8], while skeletal muscles involvement does not seem to be influenced by central mechanisms.

Magnetic resonance imaging (MRI) in LOPD has been used for the qualitative evaluation of the pattern of skeletal muscle involvement, and for quantitative assessment of enzyme replacement therapy (ERT) outcome [9]. MRI has been used to assess respiratory muscles also, and a significant correlation was found between diaphragm atrophy and respiratory dysfunction [10].

As a regular follow-up of the disease during ERT, our LOPD patients undergo both lower limb and trunk MRI. Trunk MRI allows the evaluations of posterior trunk muscles and anterior abdominal wall muscles, that are difficult to assess clinically, have a primarily postural function, and may be involved in respiratory function: indeed, posterior trunk muscles may be involved in inspiration [11], while anterior muscles are involved in forced expiration [12].

The aim of this study is to explore the relationship between trunk muscles involvement assessed by MRI and pulmonary function tests in LOPD.

Methods

We investigated prospectively, as part of routine follow-up, a total of 19 patients (8 females) aged 54.6 ± 18.2 years (range 25–76). LOPD was diagnosed by GAA activity on muscle biopsy/leukocytes, and confirmed by molecular genetic analysis. Clinical and demographic/genetic data of the patients are in **Supplementary Table 1**.

Muscle MRI was performed as previously described [13] by a 1.5T MRI scanner (1.5T Philips Intera and 1.5T Philips Ahieva XR Realeas). Muscles were graded according to the Mercuri score [14]. We considered two muscles of the posterior wall of the lower trunk (*Quadratus lumborum* and *Iliocostal lumborum*), and seven muscles of the anterior wall (*Multifidus, Longissimus, Iliopsoas, Rectus abdominis, Transversus abdominis, Obliquus externus abdominis, Obliquus internus abdominis*). Two independent observers blinded to the pulmonary functional information examined all scans (AP, SR).

Pulmonary function tests were performed within 48 hours from the MRI, and according to standard guidelines in the sitting and supine positions [15]. A postural drop of VC (ΔVC) equal or higher than 30% was considered expression of diaphragmatic weakness, as reported by an international statement [16]. Spirometry were performed at least three times to assure reproducibility, and the best value of FVC was used. Maximal inspiratory pressure (MIP) was measured from the functional residual capacity (FRC) in the upright position. Maximal expiratory pressure (MEP) was measured at the total pulmonary capacity. MIP and MEP maneuvers were repeated at least three times or until two identical readings were obtained [17], with patients receiving strong verbal encouragement [18]. The best values of both measurements were used.

Statistical analysis

The Shapiro-Wilk test was used to evaluate potential deviations of the analysed quantitative variables from the normal distribution ($p < 0.05$). Quantitative variables following the normal distribution were described by mean ± standard deviation (SD) or by median (25th – 75th percentiles) otherwise. The Welch's t-test was applied to test for statistically significant difference in terms of normally distributed quantitative variables between binary conditions. The Wilcoxon rank-sum test was used to test for statistically significant difference in terms of quantitative variables deviating from the normal distribution between binary conditions. Pairwise correlations were estimated by the Spearman test. The Fisher's exact test was used to test for association between categorical variables. The significance threshold for identifying statistically significant associations was set to $p < 0.008$ based on the Bonferroni correction accounting for the number of muscles for which the MRI score was evaluated (α = 0.05/6 tests).

Statistical tests were performed by the R software v. 3.1.0 (www.r-project.org/).

Results

A total of 19 patients were analyzed. Summary statistics reporting the characteristics of the analyzed patients are reported in Table 1 and Table 2 for quantitative and categorical variables respectively.

Table 1

Summary statistics of quantitative variables. Variable, analysed variable; Obs, non-missing observations; Statistics, for variables deviating from the normal distribution (Shapiro-Wilk p < 0.05) the mean va Vital Capacity, is reported in absolute value (VC), % of predictive value and

Variable	Value	Min	Max
MIP (cmH2O)	-52.23 ± 25.19	-108	-18
MEP (cmH2O)	73.92 ± 33.56	18	138
VC (L)	2.56 ± 1.48	0.75	5.17
VC %pred	64.59 ± 21.72	29	98
ΔVC (%)	32 (18, 35)	8	35

lue ± Standard Deviation (SD) is reported or median (25th – 75th percentiles) otherwise; Min, minimum value of the distribution; Max, maximum value of the distribution. MIP: maximal inspiratory pressure. MEP: Maximal expiratory pressure. VC = vital capacity. deltaVC: postural drop.

Table 2
Summary statistics of categorical variables. Variable, analysed variable; Obs, non-missing observations; value, values that the variable may assume; N (F), count and frequency of each value.

Variable	Obs.	Value	N (F)
Diaphragm > 20	17	No	3 (0.18)
		Yes	14 (0.82)
Diaphragm > 30	17	No	7 (0.41)
		Yes	10 (0.59)
External Oblique Muscle	14	Score = 0	7 (0.50)
		Score = 1	1 (0.07)
		Score = 2	1 (0.07)
		Score = 3	5 (0.36)
Internal Oblique Muscle	14	Score = 0	2 (0.14)
		Score = 1	3 (0.21)
		Score = 2	1 (0.07)
		Score = 3	8 (0.57)
Transversus Muscle	14	Score = 0	7 (0.50)
		Score = 1	1 (0.07)
		Score = 2	0 (0.00)
		Score = 3	6 (0.43)
Iliocostalis Lomborum Muscle	19	Score = 0	5 (0.26)
		Score = 1	3 (0.16)
		Score = 2	4 (0.21)
		Score = 3	7 (0.37)
Multifidus Muscle	19	Score = 0	2 (0.11)
		Score = 1	4 (0.21)
		Score = 2	6 (0.32)
		Score = 3	7 (0.37)
Longissimus Muscle	19	Score = 0	2 (0.11)
		Score = 1	4 (0.21)
		Score = 2	2 (0.11)
		Score = 3	11 (0.58)

Of note, two patients (patients 4 and 18) had severe postural drop despite normal upright VC (**Suppl Table 1**)

Results from association tests

Univariate tests were applied to evaluate:

1. The presence of statistically significant correlations between MRI measurements corresponding to the analyzed muscles and: MIP, MEP, FVC, Δ VC, FVC%
2. The presence of statistically significant associations between MRI measurements corresponding to the analyzed muscles and: Diaphragm > 20 or Diaphragm > 30

Non-parametric Spearman tests evidenced the presence of statistically significant pairwise correlations ($p < 0.008$) between MRI values corresponding to the *Internal Oblique* and *Multifidus* involvement and MIP parameter (rho = 0.85, p = 0.004 and rho = 0.75, p = 0.003 respectively). Similarly, *Internal Oblique, Multifidus* and *Longissimus* muscles were positively correlated to ΔVC values (rho = 0.86, p < 0.001; rho = 0.80, p < 0.001 and rho = 0.73, p < 0.001 respectively). Results are reported in Table 3 and graphically represented in Fig. 1. In particular, patients having MRI values ≥ 2 for these three parameters are characterized by a statistically significant increase in terms of ΔVC values with respect to those having MRI values ≤ 1 ($p < 0.008$).

Table 3
Results from non-parametric Spearman tests between RM score and respiratory parameters. Rho, correlation coefficient deriving from the Spearman correlation test.

	MIP		MEP		VC (L)		deltaVC		VC %pred	
Muscle	rho	p	rho	p	rho	p	rho	P	rho	p
Ext. Obl.	0.46	0.215	-0.64	0.064	-0.42	0.169	0.66	0.020*	-0.35	0.264
Int. Obl.	0.85	0.004**	-0.77	0.015*	-0.51	0.089	0.86	< 0.001**	-0.44	0.151
Transversus	0.46	0.215	-0.64	0.064	-0.42	0.169	0.66	0.020*	-0.35	0.264
Iliocostalis L.	0.56	0.046*	-0.35	0.248	-0.43	0.084	0.58	0.015*	-0.45	0.072
Multifidus	0.75	0.003**	-0.44	0.132	-0.53	0.029*	0.80	< 0.001**	-0.62	0.009*
Longissimus	0.63	0.021*	-0.43	0.145	-0.47	0.058	0.73	< 0.001**	-0.54	0.027*
* p < 0.05 ; ** p < 0.008, based on the Bonferroni correction for multiple testing										

Increased MRI scores for *multifidus muscle* are associated to a statistically significant increase in the probability of both diaphragm > 20 (p = 0.006) and diaphragm > 30 (p = 0.005), as shown in Table 4. Similarly, higher MRI scores for *longissimus muscle* are associated to a statistically significant increase in the probability of diaphragm > 30 (p = 0.002) (Table 4). A weaker but still consistent correlation was found with *Internal Oblique*.

Table 4

Probability of diaphragm > 20 and 30 by RM score level. Muscle, evaluated muscle; Each cell reports the number of individuals with diaphragm > 20 or > 30 within each RM score level for each muscle / the number of individuals within each RM score level for each muscle and the corresponding frequency (within brackets); p, p-value.

	Diaphragm > 20					Diaphragm > 30				
Muscle	Score = 0	Score = 1	Score = 2	Score = 3	p	Score = 0	Score = 1	Score = 2	Score = 3	p
Ext. Obl.	3/6 (0.50)	1/1 (1.00)	-	5/5 (1.00)	0.250	1/6 (0.17)	1/1 (1.00)	-	4/5 (0.80)	0.080
Int. Obl.	0/1 (0.00)	1/3 (0.33)	1/1 (1.00)	7/7 (1.00)	0.045*	0/1 (0.00)	0/3 (0.00)	0/1 (0.00)	6/7 (0.86)	0.015*
Transversus	3/6 (0.5)	1/1 (1.00)	-	5/5 (1.00)	0.250	1/6 (0.17)	1/1 (1.00)	-	4/5 (0.80)	0.080
Iliocostalis L.	1/4 (0.25)	3/3 (1.00)	4/4 (1.00)	6/6 (1.00)	0.013*	0/4 (0.00)	2/3 (0.67)	3/4 (0.75)	5/6 (0.83)	0.065
Multifidus	0/2 (0.00)	2/3 (0.67)	6/6 (1.00)	6/6 (1.00)	0.006**	0/2 (0.00)	0/3 (0.00)	4/6 (0.67)	6/6 (1.00)	0.005**
Longissimus	0/2 (0.00)	2/3 (0.67)	2/2 (1.00)	10/10 (1.00)	0.016*	0/2 (0.00)	0/3 (0.00)	1/2 (0.50)	9/10 (0.90)	0.002**

* p < 0.05

** p < 0.008, based on the Bonferroni correction for multiple testing

The correlations between upright FVC/MEP and trunk muscles was weak or quite inconsistent.

Discussion

In a previous multi-center study involving 30 patients, we found that early anterior and posterior trunk involvement occurs in LOPD, and represents a peculiar pattern, uncommon in other myopathies and thus helping the differential diagnosis among different muscle phenotypes [13]. Although trunk muscle involvement may be suspected in LOPD patients complaining of chronic lumbar pain, or with postural changes (hyperlordosis, abdominal prominence), trunk muscles are, in fact, difficult to assess by clinical examination alone; thus, muscle MRI may be used to assess and grade their involvement. But what is the clinical counterpart, or the clinical impact, if any, of trunk muscle involvement? Are there any functional correlates, beyond lumbar pain and postural changes?

The selectivity of diaphragm (compared to other respiratory muscles) involvement in LOPD is thought to be related to a possible contribution of spinal motor neurons at the cervical region [8]. In neurodegenerative motor neuron disorders such as ALS, diaphragm and axial muscles are usually involved in concomitance, due to the closeness of their relative motor neurons within the medial anterior horn spinal cord [19]. Thus, since both diaphragm and trunk muscles belong to the same group of "axial" muscles, we wondered a) whether there was a relationship between the involvement of trunk muscles and the involvement of diaphragm in pure muscle disorders also, and b) whether trunk involvement could contribute to respiratory dysfunction or influence respiratory parameters.

We have thus graded trunk muscle involvement, and compared the scores of muscle atrophy with measures of FVC, MIP, MEP, and postural drop. Two of these measures (postural drop, MIP) are more strictly dependent on a single muscle function, that is that of the diaphragm (which we did not directly assess by MRI, unlike other Authors [10].

We thus found a strong correlation between anterior and posterior trunk weakness and postural drop, as well as between MIP and posterior trunk weakness (posterior trunk muscles contribute to inspiration). On the contrary, there was no or only weak contribution of trunk muscles to forced expiration (MEP), and upright FVC was not influenced at all by trunk muscle involvement (Table 2).

The lack of correlation between upright VC and trunk weakness was rather unexpected, but may be in line with the known lack of relationship between respiratory involvement and skeletal muscles damage (and we may consider that trunk muscles behave like limb skeletal muscles).

By contrast, we found a strong correlation between postural drop of VC and both anterior and posterior trunk muscles status. The explanation requires a few deductions. First, postural drop, like MIP, are essentially diaphragmatic functions [4, 5]. Thus, how abdominal muscles, which are essentially expiratory [20], can influence diaphragm function?

Contraction of the abdominal muscles (which are rather powerful muscles), tends to pull the rib cage inwards and downwards and to push the abdominal contents upwards, elevating the diaphragm: both these actions cause expiration [21]. However, the abdominal muscles may contribute to inspiration also, or at least the correlation of both MIP and postural drop with abdominal muscles suggests that abdominal muscles may have an essential inspiratory contribute, even during tidal breathing, in LOPD patients with diaphragm weakness.

Actually, the contraction of the abdominal muscles during expiration is conventionally regarded as beneficial to the act of breathing, because the consecutive rise in abdominal pressure induces lengthening of the diaphragm [22–24].That is, by increasing the length of the diaphragmatic muscle fibers during expiration, the abdominal muscles place these fibers on a more advantageous portion of their length-tension curve, and hence the force-generating ability of the diaphragm during the subsequent inspiration would be greater than it would be otherwise [25].

Furthermore, Younes et al. [26] pointed that expiratory contraction of the abdominal muscles is a natural (automatic or spontaneous) component of the response of the normal respiratory system to greater than resting stimulation. When normal subjects increase their ventilation, such as during exercise or during hyperoxic hypercapnia, they recruit the abdominal muscles, particularly the transversus, during expiration. This response is nonspecific, since an expiratory recruitment of the abdominal muscles also occurs when normal subjects breathe against inspiratory mechanical loads [27, 28]. In the absence of expiratory flow limitation, contracting the abdominal muscles during expiration is an appropriate response to these challenges, since the associated reduction in end-expiratory lung volume allows the increased work of breathing to be shared between the inspiratory and the expiratory muscles [29]. It is possible that in LOPD patients with diaphragm weakness, this "automatic" response to the imbalance of the inspiratory load/capacity relationship is already triggered during resting breathing, even though it may be useless and induce additional energy expenditure.

Conclusion

We confirm that upright FVC is not influenced by axial (as well as skeletal) myopathy. However, trunk weakness furtherly worsens diaphragmatic function, and (given the upright/supine dissociation in VC) impairs the ability to compensate for diaphragmatic dysfunction in supine position. Detection of abdominal muscle damage by MRI may thus suggest the need of more extensive respiratory assessment, i.e. by polysomnography, even when upright VC is still within normal ranges.

Abbreviations

ALS amyotrophic lateral sclerosis

ERT enzyme replacement therapy

FRC functional residual capacity

FVC forced vital capacity

GAA alpha–glucosidase

LOPD Late Onset Pompe Disease

MEP maximal expiratory pressures

MIP maximal inspiratory pressure

MRI Magnetic resonance imaging

VC vital capacity

Declarations

Ethics approval and consent to participate

The data collected are part of the regular follow-up of patients with Pompe disease. Data collection and consent to participate was approved by the Pavia Ethical Committee (IRCCS San Matteo Foundation), reference number p-20160022743

Consent for publication

All patients gave consent to collect their demographic and clinical data and to perform clinical and MRI investigations.

Availability of data and material

Database of clinical data is available to any scientist whishing to use them (Sabrina.ravaglia@mondino.it)

Funding

Competing interests

The Authors declare that they have no competing interests.

Authors' contribution

The Author's contributions are as follows: AC, SR, CD: methodology, conceptualization of results, manuscript writing and editing; NB: interpretation of physiological data; CD, PdF: genetic analysis; AM statistical analysis; PC, SC, MP: respiratory examinations and acquisition of data; AP: muscle MRI. All Authors read and approved the final manuscript.

Acknowledgements

References

1 - A.T. Van der Ploeg, A.J. Reuser, Pompe's disease, Lancet 2008 (372) 1342–1353

2- van der Beek NA, van Capelle CI, van der Velden-van Etten KI, Hop WC, van den Berg B, Reuser AJ, et al. Rate of progression and predictive factors for pulmonary outcome in children and adults with Pompe disease. Mol Genet Metab. 2011;104:129–36

3- Muller-Felber W, Horvath R, Gempel K, Podskarbi T, Shin Y, Pongratz D, et al. Late onset Pompe disease: clinical and neurophysiological spectrum of 38 patients including long-term follow-up in 18 patients. Neuromuscul Disord 2007;17:698–706.

4- Fromageot C, Lofaso F, Annane D, Falaize L, Lejaille M, Clair B, Gajdos P, Raphaël JC. Supine fall in lung volumes in the assessment of diaphragmatic weakness in neuromuscular disorders. Arch Phys Med Rehabil. 2001 Jan;82(1):123-8. doi: 10.1053/apmr.2001.18053. PMID: 11239298.

5-Wenninger S, Greckl E, Babačić H, Stahl K, Schoser B. Safety and efficacy of short- and long-term inspiratory muscle training in late-onset Pompe disease (LOPD): a pilot study. J Neurol. 2019 Jan;266(1):133-147. doi: 10.1007/s00415-018-9112-4. Epub 2018 Nov 14. PMID: 30430231.

6- N Pellegrini N, Laforet P, Orlikowski D, Pellegrini M, Caillaud C, Eymard B, Raphael JC, Lofaso F. Respiratory insufficiency and limb muscle weakness in adults with Pompe's disease. Eur Respir J. 2005 Dec;26(6):1024-31. doi: 10.1183/09031936.05.00020005. PMID: 16319331.

7- van der Beek, C.I. van Capelle, K.I van der Velde-van Etten. Rate of progression and predictive factors for pulmonary outcome in children and adults with Pompe disease. Molecular Genetics and Metabolism 104 (2011) 129-136

8- DeRuisseau LR, Fuller DD, Qiu K, DeRuisseau KC, Donnelly WH Jr, Mah C, Reier PJ, Byrne BJ. Neural deficits contribute to respiratory insufficiency in Pompe disease. Proc Natl Acad Sci U S A. 2009 Jun 9;106(23):9419-24. doi: 10.1073/pnas.0902534106. Epub 2009 May 27. PMID: 19474295; PMCID: PMC2695054.

9- Neuromuscular imaging in inherited muscle diseases. Wattjes MP, Kley RA, Fischer D. Eur Radiol. 2010 Oct;20(10):2447-60.

10- Gaeta M, Barca E, Ruggeri P, Minutoli F, Rodolico C, Mazziotti S, Milardi D, Musumeci O, Toscano A. Late-onset Pompe disease (LOPD): correlations between respiratory muscles CT and MRI features and pulmonary function. Mol Genet Metab 2013 Nov;110(3):290-6.

11- Kendall FP, McCreary EK, Provance PG (1993). Muscles: testing and function, IV ed, Baltimore: Williams and Wilkins

12- Benditt JO. Pathophysiology of Neuromuscular Respiratory Diseases. Clin Chest Med. 2018 Jun;39(2):297-308. doi: 10.1016/j.ccm.2018.01.011. PMID: 29779590.

13- Alejaldre A, Díaz-Manera J, Ravaglia S, Tibaldi EC, D'Amore F, Morís G, Muelas N, Vílchez JJ, García-Medina A, Usón M, Martínez García FA, Illa I, PichiecchioA Trunk muscle involvement in late-onset Pompe disease: study of thirty patients. Neuromuscul Disord. 2012 Oct 1;22 Suppl 2:S148-54. doi: 10.1016/j.nmd.2012.05.011.

14- Mercuri E, Pichiecchio A, Counsell S, et al. A short protocol for muscle MRI in children with muscular dystrophies. Eur J Paediatr Neurol 2002; 6: 305-7

15- Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC.. Lung volumes and forced ventilatory flows. Eur Respir J 1993; 6: Suppl. 16, 5–40.

16- American Thoracic Society/European Respiratory Society. ATS/ERS Statement on respiratory muscle testing. Am J Respir Crit Care Med. 2002 Aug 15;166(4):518-624

17- Wilson SH, Cooke NT, Edwards RHT, Spiro SG. Predicted normal values for maximal respiratory pressures in caucasian adults and children. Thorax 1984; 39: 535–538.

18 Laporta D, Grassino A. Assessment of transdiaphragmatic pressure in humans. J Appl Physiol 1985; 58: 1469–1476

19- de Carvalho M, Pinto S, Swash M. Association of paraspinal and diaphragm denervation in ALS. Amyotroph Lateral Scler. 2010;11(1-2):63-6. doi: 10.3109/17482960902730080. PMID: 19533450.

20- Agostoni, E. & Campbell, E.J.M. (1970) The abdominal muscles. In: The Respiratory Muscles: Mechanics and Neural Control, pp. 175-180. Ed. Campbell, E.J., Agostoni, E. & Newsom-Davis, J. Lloyd-Luke, London

21- Green M and Moxham J. The respiratory muscles. Clinical Science 1985; 68,l-10

22- Grimby G, GoldmanM, MeadJ. Respiratory muscle action inferred from rib cage and abdominal V.P partitioning. J Appl Physiol 1976; 41: 739-51.

23 Goldman MD, Grimby G, Mead J. Mechanical work of breathing derived from the rib cage and abdominal V.P partitioning. J Appl Physiol 1976; 41:752-63

24 - Takasaki Y, Orr 0, Popkin J, Xie A, Bradley TO. Effect of hypercapnia and hypoxia on respiratory muscle activation in humans. J Appl Physiol 1989; 67:1776-84.

25 - Ninane V, Rypens F, Yernault JC, De Troyer A. Abdominal Muscle Use during Breathing in Patients with Chronic Airflow Obstruction. Am Rev Respir Dis 1882; 148:16-2

26 - Younes M. Determinants of thoracic excursions during exercise. In: Whipp BJ, Wasserman K, eds. Exercise. Pulmonary physiology and pathophysiology. Vol. 52. NewYork: Marcel Dekker, 1991; 1-65.)

27- De TroyerA, Estenne M, Ninane V,VanGansbeke 0, Gorini M. Transversus abdominis muscle function in humans. J Appl Physiol 1990;68:1010-6

28- Martin JG, De Troyer A. The behaviour of the abdominal muscles during inspiratory mechanical loading. Respir Physiol 1982; 50:63-73.

29 - Ninane V, Rypens F, Yernault JC, De Troyer A. Abdominal Muscle Use during Breathing in Patients with Chronic Airflow Obstruction. Am Rev Respir Dis 1882; 148:16-2
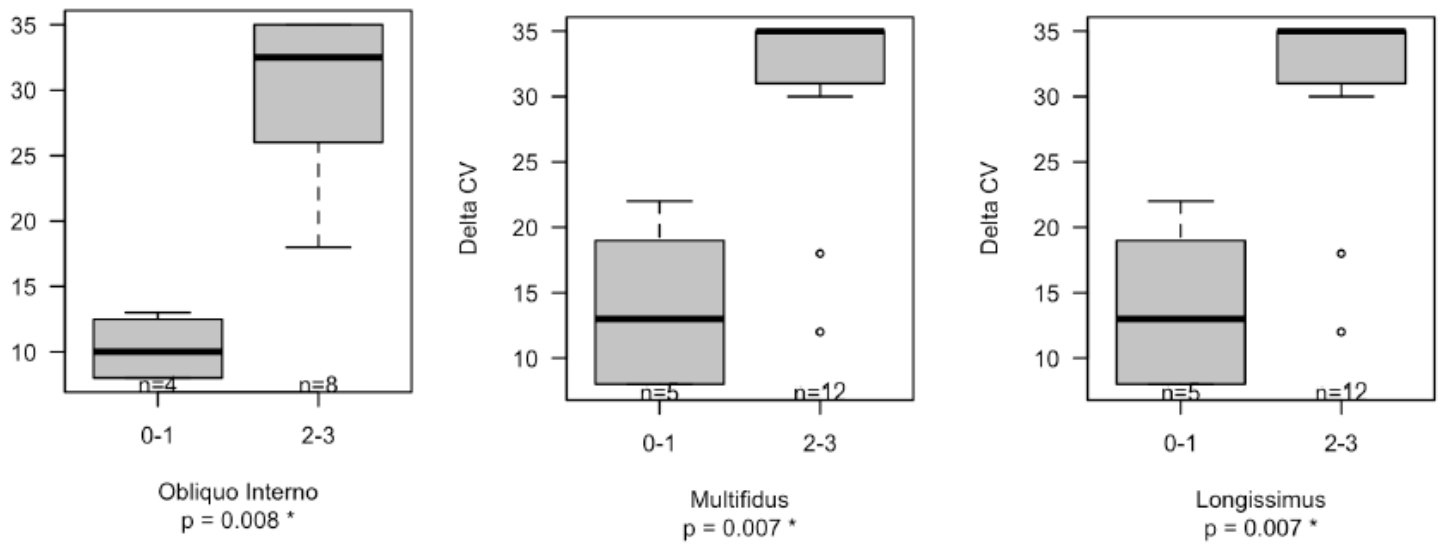
Figures

Figure 1

Results are reported in Table 3 and graphically represented in Figure 1.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplementarytable1.docx