Diurnal variations in the parameters of pulmonary function and respiratory muscle strength in patients with COPD*, **

Variação diurna de parâmetros de função pulmonar e de força muscular respiratória em pacientes com DPOC

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Abstract

Objective: To evaluate the magnitude of diurnal changes in the parameters of pulmonary function and respiratory muscle strength/endurance in a sample of patients with COPD. **Methods:** A group of 7 patients underwent spirometry, together with determination of MIP and MEP, at two distinct times (between 8:00 and 8:30 a.m. and between 4:30 and 5:00 p.m.) on a single day. Between assessments, the patients remained at rest in the laboratory. **Results:** In accordance with the Global Initiative for Chronic Obstructive Pulmonary Disease staging system, COPD was classified as moderate, severe, and very severe in 1, 3, and 3 of the patients, respectively. From the first to the second assessment, there were significant decreases in FVC, FEV_1, and MEP (of 13%, 15%, and 10%, respectively), as well as (less than significant) decreases in PEF, MIP, and maximal voluntary ventilation (of 9%, 3%, and 11%, respectively). **Conclusions:** In this sample of COPD patients, there were diurnal variations in the parameters of pulmonary function and respiratory muscle strength. The values of FEV_1, FVC, and MEP were significantly lower in the afternoon than in the morning.

Keywords: Pulmonary disease, chronic obstructive; Respiratory function tests; Respiratory muscles.

Resumo

Objetivo: Avaliar a magnitude de mudanças diurnas em parâmetros de função pulmonar e de força e resistência dos músculos respiratórios em uma amostra de pacientes com DPOC. **Métodos:** Um grupo com 7 pacientes foi submetido a espirometria e a determinação de PImáx e PEmáx em dois momentos (entre 8h00 e 8h30 e entre 16h30 e 17h00) em um único dia. Os pacientes permaneceram em repouso na área do laboratório entre as avaliações. **Resultados:** De acordo com o sistema de estadiamento da *Global Initiative for Chronic Obstructive Pulmonary Disease*, a doença foi classificada como moderada, grave e muito grave em 1, 3 e 3 pacientes, respectivamente. Da primeira para a segunda avaliação, houve uma queda significativa em CVF, VEF_1 e PEmáx (de 13%, 15% e 10%, respectivamente), bem como uma queda não significativa em PFE, PImáx e ventilação voluntária máxima (de 9%, 3% e 11%, respectivamente). **Conclusões:** Nesta amostra de pacientes com DPOC, houve variações diurnas nos parâmetros de função pulmonar e de força de músculos respiratórios. Os valores de VEF_1, CVF e PEmáx foram significativamente menores à tarde do que de manhã.

Descritores: Doença pulmonar obstrutiva crônica; Testes de função respiratória; Músculos respiratórios.

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Introduction

Spirometry and determination of maximal respiratory pressures are noninvasive methods for evaluating pulmonary function and respiratory muscle strength. The two methods are relatively simple, being frequently employed in patients with COPD.[1] Such patients might experience inspiratory and expiratory muscle weakness that can affect not only respiratory muscle strength but also expiratory flow. Inspiratory muscle weakness is related to dyspnea,[2] fatigue, and exercise limitation,[3] inspiratory muscle failure being a major cause of hypoxemia.[4] Expiratory muscle weakness has been associated with ineffective cough,[5] as well as with impaired diaphragmatic power and work. The assessment of respiratory muscle strength and pulmonary function in COPD patients is useful and relevant for monitoring the natural history of the disease.[6]

Circadian rhythms have been detected in several human organs, including the lung. Such rhythms seem to optimize common physiological functions and are regulated by peripheral circadian oscillators in the organs.[7,8] Although the existence of a circadian rhythm in pulmonary function is well established in healthy subjects, the current knowledge of circadian changes in human pulmonary function is somewhat controversial and is mostly related to asthma patients.[9]

A small number of studies have investigated the pattern of pulmonary function fluctuations during the daytime hours in healthy subjects. In regard to COPD patients, there is a lack of knowledge on diurnal changes in pulmonary function and respiratory muscle strength. The objective of the present study was to evaluate a sample of COPD patients in terms of the magnitude of changes in the parameters of pulmonary function and respiratory muscle strength/endurance, which were assessed at two distinct times on a single day.

Methods

All of the patients invited to participate in the present study had to meet the following inclusion criteria: having been diagnosed with COPD in accordance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines[10]; being a former smoker; having negative bronchodilator test results; and having been clinically stable for at least 6 months. The study was approved by the local research ethics committee, and written informed consent was given by all of the patients. The patients underwent pulmonary function testing, together with determination of MIP and MEP, at two different times (between 8:00 and 8:30 a.m. and between 4:30 and 5:00 p.m.) on a single day. Between tests, the participants remained at rest in a comfortable room. They were allowed to read or walk in a garden around the laboratory and were served a meal during the period between tests. A maximum of two individuals were studied on the same day. All of the patients took their regular medications on the day of the tests. Pulmonary function was assessed in accordance with the technical procedures and acceptability/reproducibility criteria recommended by the Brazilian Thoracic Association.[11] Spirometry was carried out with a Pony Graphics spirometer (Cosmed, Rome, Italy), FEV_1, FVC, PEF (derived from an FVC maneuver), and maximal voluntary ventilation (MVV) having been measured. All of the subjects were instructed on how to perform the procedures, which were performed with the subjects sitting in a comfortable chair and wearing a nose clip. The subjects were instructed to breathe through a disposable cardboard mouthpiece (placed between the teeth), which was carefully checked by a technician in order to avoid air leaks during the spirometric maneuvers. The subjects were asked to perform a maximal inspiratory maneuver (near TLC), followed by a maximal expiratory maneuver (near RV). A maximum of eight attempts were made by each subject, and we selected the three best (i.e., those in which the variation in the results was lower than 5% or 200 mL). We measured MVV with the patients inhaling and exhaling at maximal voluntary effort for 12-15 s and sustaining a respiratory frequency of 70-100 breaths/min. The absolute and relative values of FEV_1, FVC, and FEV_1/FVC ratio were analyzed. The FEV_1/FVC ratio was obtained by comparing the values with normal curves for all spirometric variables, as well as with reference values.[12] We evaluated respiratory muscle strength by determining MIP and MEP, in accordance with the Brazilian Thoracic Association guidelines,[11] reference values for adults in Brazil[13] having been used. With the subjects in a sitting position and wearing a nose clip, MIP was measured at RV, whereas MEP was measured at TLC. Five to eight maneuvers

were carried out until two reproducible maximal values were obtained.

Because of the small sample size, we used nonparametric descriptive statistics. The results are expressed as medians and interquartile ranges, and the Wilcoxon signed rank test was used in order to compare FVC, FEV_1, PEF, MIP, MEP, and MVV. The data were analyzed with the Statistical Package for the Social Sciences, version 15.0 (SPSS Inc., Chicago, IL, USA), and the program GraphPad Prism, version 4 (GraphPad Software Inc., San Diego, CA, USA). The significance level was set at $p < 0.05$, and all of the tests were two-tailed.

Results

We invited 12 patients to take part in the study. Of those, 5 were excluded for the following reasons: having declined to participate in the study because of a lack of interest (n = 2); and having withdrawn from the study after the first assessment (n = 3). The final sample therefore comprised 7 male patients. The baseline characteristics of the participants are summarized in Table 1. Most of the patients showed moderate to severe airflow obstruction and normal body mass index. In accordance with the GOLD staging system, COPD was classified as moderate, severe, and very severe in 1, 3, and 3 of the patients, respectively.

Regarding diurnal variations in pulmonary function parameters, we observed that there were significant decreases in FVC and FEV_1 (of 13% and 15%, respectively) from the first to the second assessment. Although there was a 9% decrease in PEF from the first to the second assessment, the difference was not significant. Table 2 and Figure 1 summarize the main findings. In the present study, MIP, MEP, and MVV (in % of predicted) were found to be 67.7%, 129.2%, and 49.3%, respectively. Although inspiratory muscle strength was found to be below normal and expiratory muscle strength was not, there was a significant decrease in MEP (of 10%) from the first to the second assessment, as well as less than significant decreases in MIP and MVV (of 3% and 11%, respectively). These results are summarized in Table 2 and Figure 2.

Discussion

We found that the parameters of pulmonary function (FVC and FEV_1) and expiratory muscle strength decreased significantly from 8:00 a.m. to 5:00 p.m. This finding supports our hypothesis that there are diurnal variations in pulmonary function and respiratory muscle strength in patients with COPD. For the present study, the patients were asked to remain in the laboratory for at least nine hours. We believe that this is the reason of the unexpectedly high dropout rate, which is a relevant limitation of the study.

Diurnal variations in respiratory physiology are well documented. The suprachiasmatic nucleus, located in the anterior hypothalamus, is the main circadian pacemaker in humans, driving circadian rhythms of behavior and activity of most organs.[14,15] Previous investigations have documented the relationship between diurnal variations in respiratory physiology and obstructive pulmonary diseases.[16,17] Israels was the first author to report differences between diurnal and nocturnal values of FEV_1 and FVC in hospitalized patients with asthma or bronchitis, as well as in healthy subjects.[18] That author found decreased nocturnal values of FVC and FEV_1 in the hospitalized patients and healthy subjects, no worsening of the symptoms having been observed in the former and no

Table 1 - Anthropometric and respiratory characteristics of the COPD patients studied.

Patients	Age, years	BMI, kg/m^2	FVC, % of predicted	FEV_1, % of predicted	FEV_1/FVC, % of predicted
1	63	26.2	29,4	19.40	31.3
2	75	26.3	45.1	45.66	51.1
3	68	24.2	43.4	60.95	68.0
4	72	23.6	28.7	29.47	50.6
5	66	25.7	46.3	48.15	49.8
6	67	24.2	45.8	28.95	30.4
7	68	23.6	33.1	34.52	50.3
Median	68	24.2	43.4	34.00	50.0
IQR	66-72	23.6-26.2	29.4-45.8	29.2-48.1	31.1-51.1

BMI: body mass index; and IQR: interquartile range.

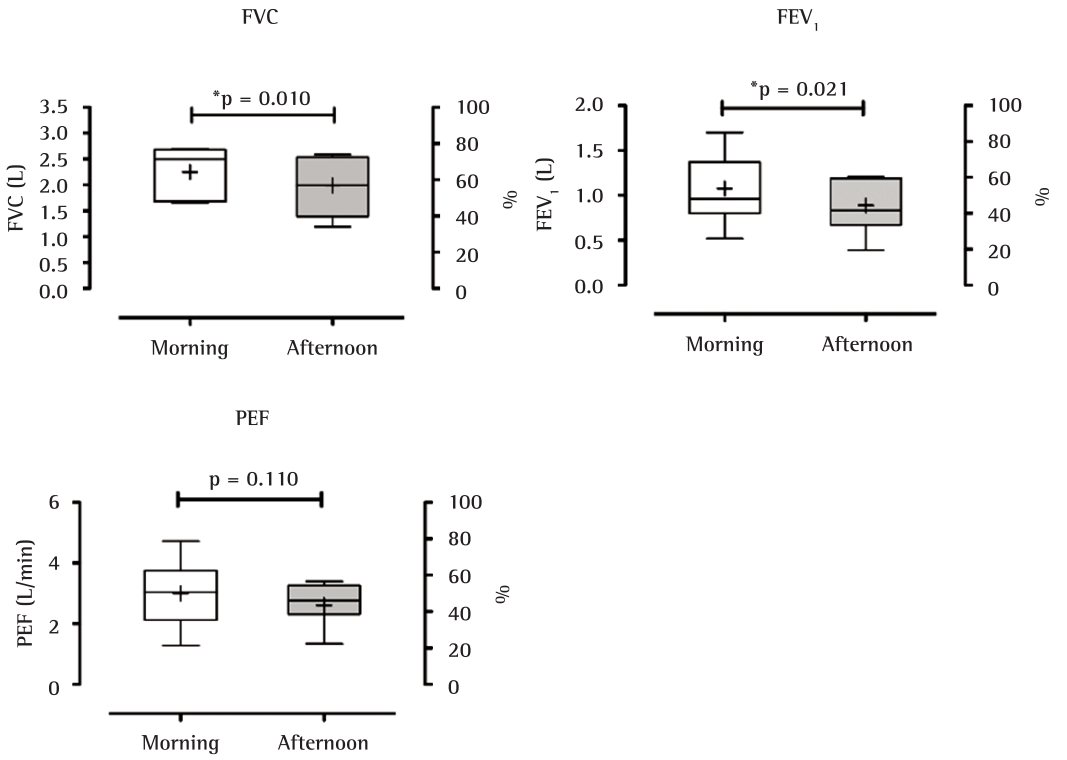

Figure 1 - Comparison of FVC, FEV_1, and PEF values measured in the morning (light gray) and in the afternoon (dark gray). The solid lines represent the medians, and the crosses represent the mean. *p < 0.05.

significant differences between diurnal and nocturnal values having been observed in the latter. In another study, one group of authors[19] investigated the magnitude of variations in FVC and FEV_1 between 10 p.m. and 6:00 a.m. in 5 healthy male subjects and 16 male patients with obstructive airway disease, which was severe in 12. The authors found that FVC and FEV_1 were lowest at 6:00 a.m. in both groups, having reported that relatively large spontaneous variations in FVC and FEV_1 occurred between 9:00 a.m. and 5:00 p.m. It is difficult to evaluate that study because all of the results were presented as figures.[19] The patients included in that study formed a heterogeneous group with chronic bronchitis or emphysema (with or without asthma), and, during the study period, none of the patients were under pharmacological treatment, which precludes the comparison between our results and those of that study. McCarley et al.[20] studied airway patency (as measured by PEF) in COPD patients, using cosinor analysis and describing the circadian rhythm of PEF on 8 consecutive days (at 11:00 a.m., 3:00 p.m., and 7:00 p.m.). Of the 10 patients investigated in that study, 6 displayed circadian rhythms for PEF, and population-mean cosinor analysis showed a significant circadian rhythm, the amplitude being 4%. Casale et al. used the same methodology and measured PEF every two hours over an entire day (from midnight to 6:00 p.m. and from 6:00 p.m. to midnight), mean cosinor analysis having revealed a PEF amplitude of 17.2%.[21] In the present study, PEF amplitude was 10.96%, halfway between the results reported in those studies.[20,21] These discrepant findings might be due to the different analytical methods employed in the studies. We did not use cosinor analysis. In addition, we assessed PEF derived from an FVC maneuver, as did Casale et al.[21] In contrast, McCarley et al.[20] assessed PEF using a peak flow meter. However, two previous studies[22,23] demonstrated that the difference between the two methods for measuring PEF (i.e., with a spirometer or a peak flow meter) is small and clinically insignificant. In a previous study, Teramoto et al.[24] evaluated variations in spirometric parameters in COPD patients over a 12-h period. The authors measured FEV_1 and PEF

Table 2 - Parameters of pulmonary function and respiratory muscle strength/endurance assessed at two distinct times (in the morning and in the afternoon) on a single day in the COPD patients under study.[a]

Variables	Morning	Afternoon
FVC, L	2.50 (1.68-2.68)	1.99 (1.39-2.53)*
FEV_1, L	1.24 (0.72-1.34)	0.96 (0.87-1.37)*
PEF, L/min	3.10 (2.12-3.75)	2.76 (2.32-3.26)
MVV, L/min	56.8 (39.2-79.7)	43.9 (36.9-61.1)
MEP, cmH_2O	145.0 (131.7-147.6)	113.0 (106.3-130.9)*
MIP, cmH_2O	69.3 (56.0-106.8)	63.7 (60.0-94.0)

MVV: maximal voluntary ventilation. [a]Values expressed as median (interquartile range). *p < 0.05.

at three distinct times during the daytime and found a coefficient of variation of 6.6% for FEV_1 and of 7.5% for PEF. We cannot compare these results with those obtained in the present study, given that those authors did not describe their findings clearly; data were presented in a graphic form, and only the coefficient of variation was shown. In addition, the statistical procedure used in order to obtain the coefficient of variation was not described.

Maximal respiratory pressures and MVV are the clinical parameters that are most commonly used in order to assess respiratory muscle strength and endurance, the measurement of those parameters constituting a practical method for clinical evaluation. In the present study, inspiratory muscle strength was found to be below the predicted value (67.7% of predicted), whereas expiratory muscle strength was not (129.2% of predicted). However, we found a significant decrease in MEP, not in MIP. These results are not surprising, given that the ability of the diaphragm to generate pressure has been reported to be preserved in COPD patients.[25] In addition, levels of neural respiratory drive in COPD patients have been reported to be three times as high as those

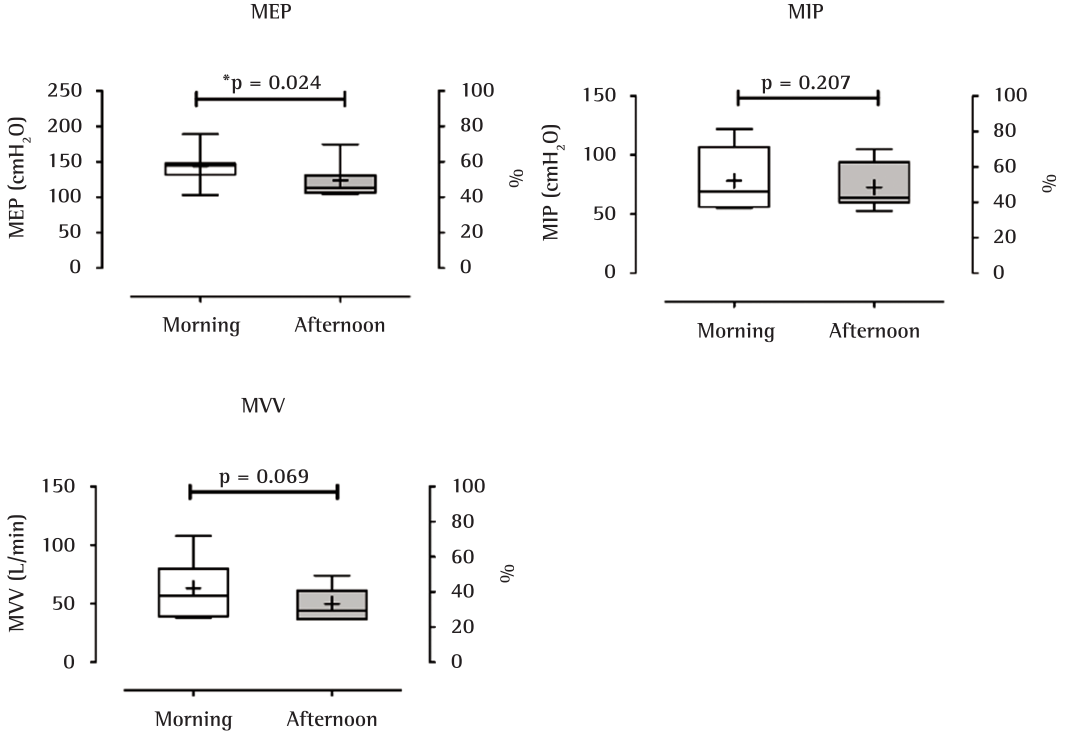

Figure 2 - Comparison of MIP, MEP, and maximal voluntary ventilation (MVV) values measured in the morning (light gray) and in the afternoon (dark gray). The solid lines represent the medians, and the crosses represent the mean. *p < 0.05.

in healthy subjects.[26] This suggests that the inspiratory muscles of COPD patients remain relatively resistant to the development of fatigue.[26,27] The expiratory muscles of COPD patients are often active,[28] and previous studies have shown that expiratory muscle strength and endurance are decreased.[29] Teramoto et al.[24] investigated the variations in maximal respiratory pressures in COPD patients, the methods employed in the study having been described above. The authors performed three assessments within a span of 12 h and found no significant differences between MIP and MEP values, the coefficients of variation for MIP and MEP being 8.5% and 6.6%, respectively. As previously mentioned, the data analysis methods employed by Teramoto et al.[24] differed from those employed in the present study, which precludes the comparison between their results and our results.

The small sample size is the major limitation of the present study. The sample size was small because of time constraints and the unexpectedly high dropout rate. Therefore, care should be taken in extrapolating the results. However, our results offer a new perspective on diurnal variations in the parameters of pulmonary function and respiratory muscle strength in COPD patients.

The results of the present study suggest that pulmonary function and respiratory muscle strength/endurance change during the daytime in patients with COPD, the values of FEV_1, FVC, and MEP having been significantly lower in the afternoon than in the morning in the COPD patients investigated in the present study.

References

1. Fiz JA, Montserrat JM, Picado C, Plaza V, Agusti-Vidal A. How many manoeuvres should be done to measure maximal inspiratory mouth pressure in patients with chronic airflow obstruction? Thorax. 1989;44(5):419-21. PMid:2763242. PMCid:461850. http://dx.doi.org/10.1136/thx.44.5.419
2. Killian KJ, Jones NL. Respiratory muscles and dyspnea. Clin Chest Med. 1988;9(2):237-48. PMid:3292125.
3. Gosselink R, Troosters T, Decramer M. Peripheral muscle weakness contributes to exercise limitation in COPD. Am J Respir Crit Care Med. 1996;153(3):976-80. PMid:8630582.
4. Bégin P, Grassino A. Inspiratory muscle dysfunction and chronic hypercapnia in chronic obstructive pulmonary disease. Am Rev Respir Dis. 1991;143(5 Pt 1):905-12. PMid:8630582.
5. Arora NS, Gal TJ. Cough dynamics during progressive expiratory muscle weakness in healthy curarized subjects. J Appl Physiol. 1981;51(2):494-8. PMid:7263456.
6. Kerstjens HA, Rijcken B, Schouten JP, Postma DS. Decline of FEV1 by age and smoking status: facts, figures, and fallacies. Thorax. 1997;52(9):820-7. PMid:9371217. PMCid:1758654. http://dx.doi.org/10.1136/thx.52.9.820
7. Sangoram AM, Saez L, Antoch MP, Gekakis N, Staknis D, Whiteley A, et al. Mammalian circadian autoregulatory loop: a timeless ortholog and mPer1 interact and negatively regulate CLOCK-BMAL1-induced transcription. Neuron. 1998;21(5):1101-13. http://dx.doi.org/10.1016/S0896-6273(00)80627-3
8. Cardone L, Hirayama J, Giordano F, Tamaru T, Palvimo JJ, Sassone-Corsi P. Circadian clock control by SUMOylation of BMAL1. Science. 2005;309(5739):1390-4. PMid:16109848. http://dx.doi.org/10.1126/science.1110689
9. Hetzel MR. The pulmonary clock. Thorax. 1981;36(7):481-6. PMid:7031967. PMCid:1020426. http://dx.doi.org/10.1136/thx.36.7.481
10. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS; GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med. 2001;163(5):1256-76. PMid:1131666.
11. Sociedade Brasileira de Pneumologia e Tisiologia. Diretrizes para testes de função pulmonar. J Pneumol. 2002;28(3):S1-238.
12. Pereira CA, Sato T, Rodrigues SC. New reference values for forced spirometry in white adults in Brazil. J Bras Pneumol. 2007;33(4):397-406. PMid:1798253. http://dx.doi.org/10.1590/S1806-37132007000400008
13. 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(6):719-27. http://dx.doi.org/10.1590/S0100-879X199900060000
14. Gibbs JE, Beesley S, Plumb J, Singh D, Farrow S, Ray DW, et al. Circadian timing in the lung; a specific role for bronchiolar epithelial cells. Endocrinology. 2009;150(1):268-76. Cvs. PMid:18787022. http://dx.doi.org/10.1210/en.2008-0638
15. Reppert SM, Weaver DR. Molecular analysis of mammalian circadian rhythms. Annu Rev Physiol. 2001;63:647-76. PMid:11181971. http://dx.doi.org/10.1146/annurev.physiol.63.1.647
16. Jarjour NN. Circadian variation in allergen and nonspecific bronchial responsiveness in asthma. Chronobiol Int. 1999;16(5):631-9. PMid:10513886. http://dx.doi.org/10.3109/07420529908998732
17. Martin RJ. Location of airway inflammation in asthma and the relationship to circadian change in lung function. Chronobiol Int. 1999;16(5):623-30. PMid:10513885. http://dx.doi.org/10.3109/07420529908998731
18. Israels AA. Asthma Bronchiale, Etterige (Bacteriele Bronchitis) En et Endocriene Systeem [dissertation]. Grönigen: Faculty of Medical Sciences; 1951.
19. Lewinsohn HC, Capel LH, Smart J. Changes in forced expiratory volumes throughout the day. Br Med J. 1960;1(5171):462-4. PMid:14416484. PMCid:1967039. http://dx.doi.org/10.1136/bmj.1.5171.462
20. McCarley C, Hanneman SK, Padhye N, Smolensky MH. A pilot home study of temporal variations of symptoms in chronic obstructive lung disease. Biol Res Nurs. 2007;9(1):8-20. PMid:17633443. http://dx.doi.org/10.1177/1099800407303501
21. Casale R, Pasqualetti P. Cosinor analysis of circadian peak expiratory flow variability in normal subjects, passive

smokers, heavy smokers, patients with chronic obstructive pulmonary disease and patients with interstitial lung disease. Respiration. 1997;64(4):251-6. PMid:9257358. http://dx.doi.org/10.1159/000196682
22. Wensley D, Pickering D, Silverman M. Can peak expiratory flow be measured accurately during a forced vital capacity manoeuvre? Eur Respir J. 2000;16(4):673-6. PMid:11106211. http://dx.doi.org/10.1034/j.1399-3003.2000.16d18.x
23. Agarwal D, Gupta PP. A comparison of peak expiratory flow measured from forced vital capacity and peak flow meter manoeuvres in healthy volunteers. Ann Thorac Med. 2007;2(3):103-6. PMid:19727355. PMCid:2732084. http://dx.doi.org/10.4103/1817-1737.33697
24. Teramoto S, Suzuki M, Matsui H, Ishii T, Matsuse T, Ouchi Y. Influence of age on diurnal variability in measurements of spirometric indices and respiratory pressures. J Asthma. 1999;36(6):487-92. PMid:10498043. http://dx.doi.org/10.3109/02770909909054554
25. Similowski T, Yan S, Gauthier AP, Macklem PT, Bellemare F. Contractile properties of the human diaphragm during chronic hyperinflation. N Engl J Med. 1991;325(13):917-23. PMid:1881417. http://dx.doi.org/10.1056/NEJM199109263251304
26. Jolley CJ, Luo YM, Steier J, Reilly C, Seymour J, Lunt A, et al. Neural respiratory drive in healthy subjects and in COPD. Eur Respir J. 2009;33(2):289-97. PMid:18829678. http://dx.doi.org/10.1183/09031936.00093408
27. McKenzie DK, Butler JE, Gandevia SC. Respiratory muscle function and activation in chronic obstructive pulmonary disease. J Appl Physiol. 2009;107(2):621-9. PMid:19390004. http://dx.doi.org/10.1152/japplphysiol.00163.2009
28. Ninane V, Rypens F, Yernault JC, De Troyer A. Abdominal muscle use during breathing in patients with chronic airflow obstruction. Am Rev Respir Dis. 1992;146(1):16-21. PMid:1385684.
29. Ramírez-Sarmiento A, Orozco-Levi M, Barreiro E, Méndez R, Ferrer A, Broquetas J, et al. Expiratory muscle endurance in chronic obstructive pulmonary disease. Thorax. 2002;57(2):132-6. PMid:11828042. PMCid:1746253. http://dx.doi.org/10.1136/thorax.57.2.132

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