



“Effects of L-Menthol in Controlling Exercise Induced Dyspnea and Fatigue Among COPD Patients”

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ABSTRACT:

Objective–To find out the effects of L-Menthol in controlling exercise induced dyspnea and fatigue among chronic obstructive pulmonary disease patients.

Method- 120 subjects whose inclusion criteria were matching were enrolled for the study. Patients were selected via convenient sampling method .Procedure was explained and informed consent was filled.

Then baseline data [Borg’s dyspnea scale, Borg’s rating of perceived exertion scale, SPO2 and Pulse rate] was recorded. Then patient was instructed to perform the stair climb power test [9 steps] and two repetitions were done and time was recorded for each .After both repetitions, again base line data was recorded , At the same time , L-MENTHOL was administered to the patient for 1minute. Again, baseline data was recorded

Result and Conclusion-Correlation between 1st and 2nd reading of stair climb test was significant with different pre, post test , variables such as BDS , BRPE, SPO2 , L-MENTHOL ,PULSE RATE. Comparison between Pretest, Post test & After L-menthol, BDS, BRPE, PR, SpO2 was significant.

Introduction

Chronic Obstructive Pulmonary Disease [COPD] is a common preventable and treatable disease which affects men and women worldwide and its abnormalities in the small airways of the lungs cause limitations of airflow in and out of the lungs.^[1] There may be damage to certain parts of the lung, sputum blocking the air passage and inflammation in the lining of airways.^[1] Its complications associated with health are exercise intolerance, physical inactivity^[2] disturbed physiological status^[3] death rate ^[4]and decreased overall human health.^[5] COPD imposes a substantial burden on majority of patients including a range of symptoms such as dyspnea and fatigue.^[6,7,8]

Dyspnea is a primary symptom experienced by COPD

patients.^[9] In chronic cases, dyspnea reduces the participation in physical activity with negative impact on quality of life and increase in death rate ^[10,11]

Fatigue is a psychological feeling of muscle tiredness and is another most common symptom experienced by COPD patients. ^[12] Fatigue is not relevant to the degree of airflow limitation.^[13] This refers that the degree of airflow limitation is not the underlying cause of mild to severe fatigue experienced by COPD patients. However, COPD can increase the severity of signs and symptoms which lead to fatigue from mild to severe.^[14,15] Diminished gas exchange will result into low levels of oxygen saturation.^[16]

In terminal stages of COPD, patients present with abnormalities of gases interchange either with



hypercapnia along with hypoxemia or hypoxemia alone.^[17,18] Approx 7% of patients develop resting hypoxemia within 5 years and patients who do not develop resting hypoxemia become hypoxemic while exercising or sleeping.^[19,20,21] The severity of hypoxemia is related to mortality in COPD.^[22]

COPD patients experience an increase in heart rate^[23,24], ischemic heart disease, arrhythmias, heart failure are most commonly seen in COPD patients.^[23]

L-Menthol is a natural cooling receptor which proposes relief to decrease the perception of dyspnea by activating the TRANSIENT RECEPTOR POTENTIAL MELASTANIN 8 [TRPM8] channel in the sensory nerve fibers of the tongue thus encouraging the cooling sensation which increases the cognitive inspiratory flow.^[24,25,26]

The effect of L-Menthol reduces the intensity of shortness of breath and inspiratory pattern flow resistance and breathing difficulties due to issues in elastic recoil with no significant changes in ventilation.^[27]

L-Menthol odor stimulation provides stimulus to decrease the levels of breathing difficulties and tightness of the chest in patients with COPD.^[28]

Methodology

The study design and sampling criteria was convenient sampling, which was done in Moradabad, Uttar Pradesh

The selection criteria included :

Inclusion criteria– Age group between 40- 60 years [conscious COPD subjects] females and males

Exclusion criteria - Subjects having acute exacerbation within 3 weeks. Subjects on any kind of supplemental

oxygen or any recent surgery, walking abnormalities, Neuromuscular issues , Sensory issues, Subjects below 35years and above 75years

Procedure

Total 120 subjects were taken based on inclusion and exclusion criteria and consent form was filled before starting the study. Data was collected mainly from TMU hospital of Moradabad and few subjects were enrolled from the nearby areas. Written informed consent was also taken from each subject. The procedure was explained and demonstrated to the subjects and it was as follows:

- Therapist marked the 9 steps on stairs then therapist measured the base line data (Borg's dyspnea scale and Borg's rating of perceived scale and recorded the pulse rate and SPO₂).
- Subjects were instructed to climb 9 steps on stairs and while climbing the stairs, therapist gave support and recorded the time of patient in which each subject climbed with the help of stopwatch, and at 10th stair, therapist made the patient sit to give rest for 10 seconds and then recorded the base line data (Borg's dyspnea scale, Borg's rating of perceived exertion, pulse rate and SpO₂)
- L-Menthol was administered to the subject then again subject climbed the 9 step of stairs and the same procedure was continued.

Results

120 subjects participated out of which 83 were females and 37 were males.

The result came out as:

“Table 1: Correlation between 1st and 2nd reading of stair climb test with different pre and post test variables”

Correlation between 1 st and 2 nd reading of stair climb test with different pre and post test variables		
VARIABLES	1ST READING OF STAIR CLIMB TEST (P-value)	2ND READING OF STAIR CLIMB TEST (P-value)
Pre test BDS	0.115	0.04
Post test BDS	0.001	0.001
After L-menthol BDS	0.444	0.768
Pre test BRPE	0.613	0.916
Post test BRPE	0.003	0.005
After L-menthol BRPE	0.008	0.026



Pre test SPO2	0.303	0.036
Post test SPO2	0.018	0.013
After L-menthol SPO2	0.056	0.099
Pre test PR	0.001	0.001
Post test PR	0.001`	0.001
After L-menthol PR	0.001	0.001

Table 1 shows the co-relation between 1st reading and 2nd reading of stair climb test. It was found significant with different pre and post-test variables such as BDS, BRPE, SPO2, L-MENTHOL, PULSE RATE. This was done through Pearson correlation coefficient test.

“Figure 1: Correlation between 1st and 2nd reading of stair climb test with different pre and post test variables”

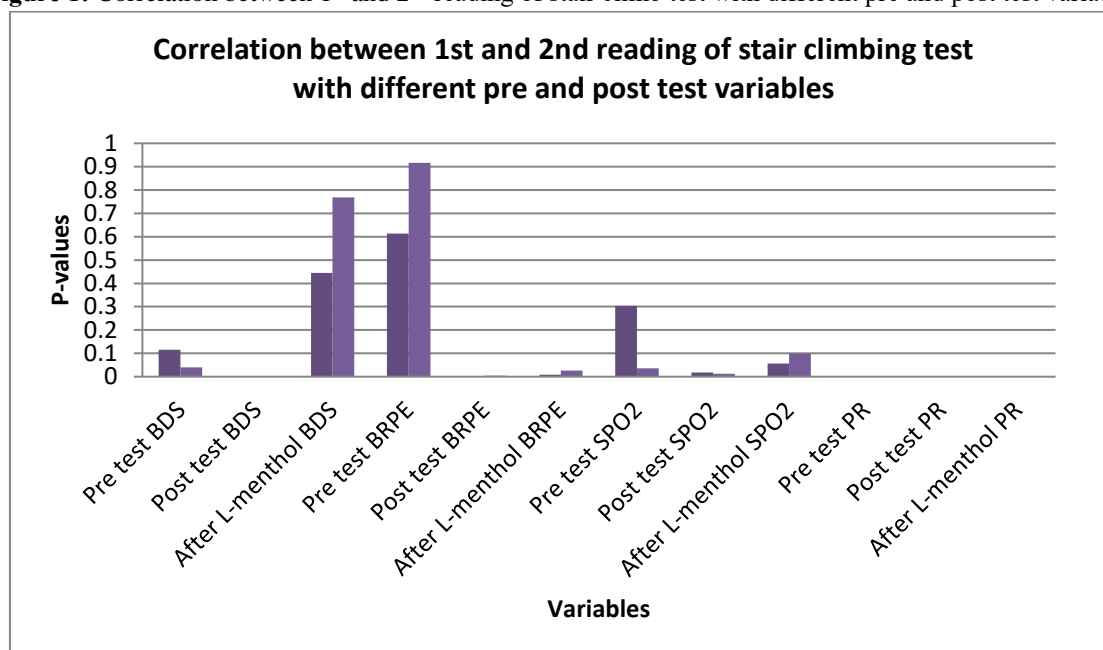


Figure 1 shows the co-relation between 1st reading and 2nd reading of stair climb test. It was found significant with different pre and post-test variables such as BDS, BRPE, SPO2, L-MENTHOL, PULSE RATE

“Table 2: Comparison between Pre-test, Post-test and After L-menthol variables with BDS, BRPE, SPO2 and PR”

Comparison between Pre test, Post test and After L-menthol variables with BDS, BRPE, SPO2 and PR				
Variables	BDS	BRPE	PR	SPO2
Pre test	0.001	0.001	0.001	0.001
Post test	0.001	0.001	0.001	0.001
After L-menthol	0.001	0.001	0.001	0.001

Table 2 shows the comparison between Pre test, Post test & After L-menthol variables with BDS, RPE, Pulse rate and SPO2 separately. It was calculated through ANOVA TEST and the result was significant.



“Figure 2: Comparison between Pre-test, Post-test and After L-menthol variables with BDS, BRPE, SPO2 and PR”

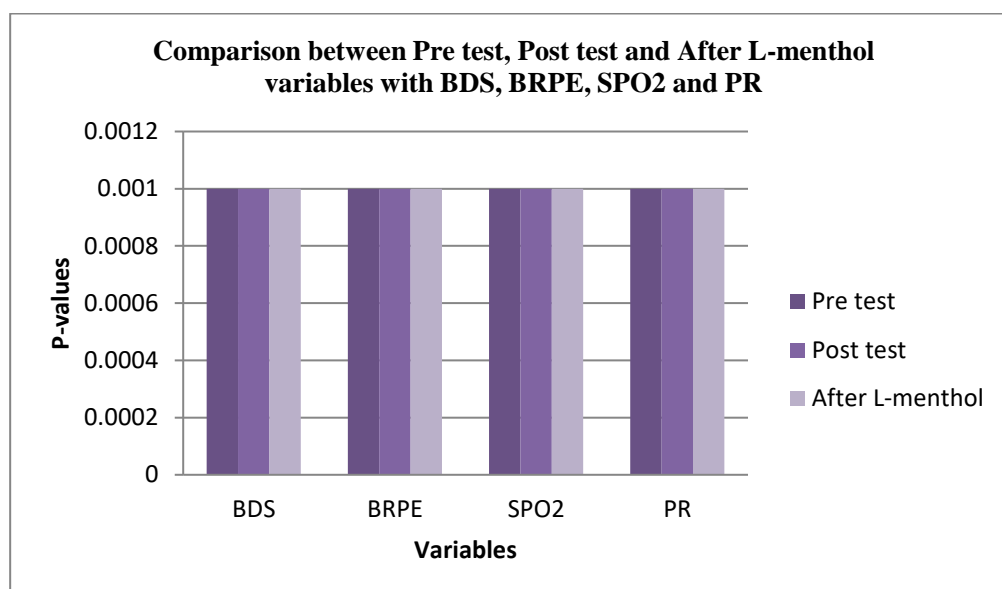


Figure 2 shows the comparison between Pre test, Post test & After L-menthol variables with BDS, BRPE, Pulse rate and SPO2 separately.

Discussion

The current study was performed to examine the effects of L-MENTHOL in controlling exercise induced dyspnea and fatigue among COPD patients.

Hammad Quershi et.al in 2014 explained that COPD is a common preventable disease and identified by persistent airflow limitation which is usually progressive in nature and there is enhancement in inflammatory response in the airways and the lungs to noxious particles^[29] Impact of COPD exacerbation is identified by change in symptoms like dyspnea and fatigue^[30].

Louis Lavolette Pierantino et. Al in 2014 explained that dyspnea is a subjective feeling of uneasy breathing that includes qualitative sensation that are different in intensity^[31,32,33] and sometimes pressure of pain is seen in quarter of the general population^[34,35].

In current study we have seen significant result in sensation of breathlessness after administration of L-menthol.

Yvonne M J et.al in 2018 explained that fatigue is a subjective feeling which consists of tiredness or exhaustion and is present next to dyspnea and is also common in patients with COPD^[36] which results in loss of ability to perform activities of daily life^[37,38].

Prevalence is seen greater in elderly^[39]. In our current study we have seen significant results in fatigue after administration of L-menthol

John B west et.al in 2011 explained that Diminished gas exchange will result into low levels of oxygen saturation^[16]. In our current study we have seen significant result in SPO2 after administration of L-menthol.

Debasree Banerjee et.al in 2017 explained that the modified Borg's dyspnea scale is a tool which is 0-10 marked numerical score used to identify sensation of breathlessness as complained by the subjects^[40], that is why we have used this tool to measure dyspnea in our study.

Guillaume Prieur et.al in 2021 explained that L-Menthol is a natural cooling receptor which proposes relief to decrease the perception of dyspnea by activating the TRANSIENT RECEPTOR POTENTIAL MELASTANIN 8 [TRPM8] channeling the sensory nerve fibers of the tongue thus encouraging the cooling sensation which further increases the cognitive inspiratory flow.^[19,20,21] In our current study we have used L-menthol to identify its effects in controlling exercise induced dyspnea and fatigue.

Takashi Nishino et.al in 1997 explained that the effect of



L-Menthol by nasal inhalation reduces the intensity rating of shortness of breath and inspiratory pattern flow resistance and elastically filled breathing difficulties with no significant changes in ventilation^[22]. In our study we have given oral stimulation of L-menthol and seen significant results on primary symptoms of COPD [dyspnea and fatigue].

Conclusion

In this current study, COPD subjects were enrolled as per inclusion and exclusion criteria and effect of L-menthol was given to reduce exercise induced dyspnea and fatigue. 120 subjects were enrolled in the study and readings of different variables were taken. Correlation between stair climb test reading 1 and 2 with different pre and post-test scales was found out through Pearson's correlation coefficient test. There was statistically significant correlation between stair climb test reading 1 with Post-test BDS, Post-test BRPE, After L-menthol BRPE, Post-test SpO₂, after L-menthol SpO₂, Pre-test PR, Post-test PR and after L-menthol PR. There was statistically significant correlation between stair climb test reading 2 Pre-test BDS, Post-test BDS, Post-test BRPE, after L-menthol BRPE, Pre-test SpO₂, Post-test SpO₂, after L-menthol SpO₂, Pre-test PR, Post-test PR and after L-menthol PR.

Comparison between various readings was found out through ANOVA and was statistically significant with p value of 0.001 for each:

- Pretest, Posttest and after L-menthol BDS
- Pretest, Posttest and after L-menthol BRPE
- Pretest, Posttest and after L-menthol SpO₂
- Pretest, Posttest and after L-menthol PR

The result was statistically significant for most of the variables which proves that L-menthol has a positive impact in reducing exercise induced dyspnea and fatigue among COPD subjects.

Clinical Relevance

Clinical relevance says that it is very important to work on the exercise induced dyspnea and fatigue of COPD subjects for making good rehabilitation protocol.

L-menthol which is used in the study creates a positive impact and thus helps in improving quality of life of the subjects.

Advantages of the Study

- It is cost effective

- Easy to administer

One of the main advantages is that it does not take much time to administer L-menthol and just a small piece of L-menthol creates a positive impact in improving patient's whole life thus motivating him to do better in all the daily life aspects.

Limitations of the Study

- One of the main limitations of the study was, patient was not able to cooperate with the therapist in terms of stair climbing due to pain or other deformities whatsoever.
- Patients were also hesitant to take L-menthol orally.
- Study was for a very short duration.

Future Scope

Future studies should focus on adding L-menthol to the patient's rehabilitation protocol and study should be done for a longer duration to aid better result.

Conflict of Interest

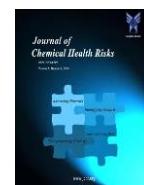
There was no conflict of interest reported among all the authors of this clinical study.

References

1. World Health Organization. *Chronic obstructive pulmonary disease (COPD)*. World Health Organization: WHO. [https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-\(copd\)](https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd)).
2. Garcia-Rio, F.; Lores, V.; Mediano, O.; Rojo, B.; Hernanz, A.; López-Collazo, E.; Alvarez-Sala, R. Daily Physical Activity in Patients with Chronic Obstructive Pulmonary Disease Is Mainly Associated with Dynamic Hyperinflation. *American Journal of Respiratory and Critical Care Medicine* **2009**, *180* (6), 506–512. <https://doi.org/10.1164/rccm.200812-1873oc>.
3. Oga, T.; Tsukino, M.; Hajiro, T.; Ikeda, A.; Nishimura, K. Analysis of Longitudinal Changes in Dyspnea of Patients with Chronic Obstructive Pulmonary Disease: An Observational Study. *Respiratory Research* **2012**, *13* (1), 85. <https://doi.org/10.1186/1465-9921-13-85>.
4. Nishimura, K.; Izumi, T.; Tsukino, M.; Oga, T. Dyspnea Is a Better Predictor of 5-Year Survival than Airway Obstruction in Patients with



- COPD. *Chest* **2002**, *121* (5), 1434–1440. <https://doi.org/10.1378/chest.121.5.1434>.
5. Stephenson, J.; Wertz, D.; Gu, T.; Patel, J.; Dalal, A. Clinical and Economic Burden of Dyspnea and Other COPD Symptoms in a Managed Care Setting. *International Journal of Chronic Obstructive Pulmonary Disease* **2017**, Volume 12, 1947–1959. <https://doi.org/10.2147/copd.s134618>.
6. Lopez, A. D.; Shibuya, K.; Rao, C.; Mathers, C. D.; Hansell, A. L.; Held, L. S.; Schmid, V.; Buist, S. Chronic Obstructive Pulmonary Disease: Current Burden and Future Projections. *The European respiratory journal* **2006**, *27* (2), 397–412. <https://doi.org/10.1183/09031936.06.00025805>.
7. Mathers, C. D.; Loncar, D. Projections of Global Mortality and Burden of Disease from 2002 to 2030. *PLoS Medicine* **2006**, *3* (11), e442. <https://doi.org/10.1371/journal.pmed.0030442>.
8. Miravittles, M.; Worth, H.; Soler Cataluña, J. J.; Price, D.; De Benedetto, F.; Roche, N.; Godtfredsen, N. S.; van der Molen, T.; Löfdahl, C.-G.; Padullés, L.; Ribera, A. Observational Study to Characterise 24-Hour COPD Symptoms and Their Relationship with Patient-Reported Outcomes: Results from the ASSESS Study. *Respiratory research* **2014**, *15* (1), 122. <https://doi.org/10.1186/s12931-014-0122-1>.
9. Parshall, M. B.; Schwartzstein, R. M.; Adams, L.; Banzett, R. B.; Manning, H. L.; Bourbeau, J.; Calverley, P. M.; Gift, A. G.; Harver, A.; Lareau, S. C.; Mahler, D. A.; Meek, P. M.; O'Donnell, D. E. An Official American Thoracic Society Statement: Update on the Mechanisms, Assessment, and Management of Dyspnea. *American Journal of Respiratory and Critical Care Medicine* **2012**, *185* (4), 435–452. <https://doi.org/10.1164/rccm.201111-2042st>.
10. Pumar, M. I.; Gray, C. R.; Walsh, J. R.; Yang, I. A.; Rolls, T. A.; Ward, D. L. Anxiety and Depression-Important Psychological Comorbidities of COPD. *Journal of Thoracic Disease* **2014**, *6* (11), 1615–1631. <https://doi.org/10.3978/j.issn.2072-1439.2014.09.28>.
11. Travis, W. D.; Costabel, U.; Hansell, D. M.; King, T. E.; Lynch, D. A.; Nicholson, A. G.; Ryerson, C. J.; Ryu, J. H.; Selman, M.; Wells, A. U.; Behr, J.; Bouros, D.; Brown, K. K.; Colby, T. V.; Collard, H. R.; Cordeiro, C. R.; Cottin, V.; Crestani, B.; Drent, M.; Dudden, R. F. An Official American Thoracic Society/European Respiratory Society Statement: Update of the International Multidisciplinary Classification of the Idiopathic Interstitial Pneumonias. *American Journal of Respiratory and Critical Care Medicine* **2013**, *188* (6), 733–748. <https://doi.org/10.1164/rccm.201308-1483st>.
12. Janson-Bjerklie, S.; Carrieri, V. K.; Hudes, M. The Sensations of Pulmonary Dyspnea. *Nursing Research* **1986**, *35* (3), 154–159.
13. Course of Normal and Abnormal Fatigue in Patients with Chronic Obstructive Pulmonary Disease, and Its Relationship with Domains of Health Status. *Patient Education and Counseling* **2011**, *85* (2), 281–285. <https://doi.org/10.1016/j.pec.2010.08.021>.
14. Determinants and Impact of Fatigue in Patients with Chronic Obstructive Pulmonary Disease. *Respiratory Medicine* **2009**, *103* (2), 216–223. <https://doi.org/10.1016/j.rmed.2008.09.022>.
15. Rodriguez-Roisin, R. Toward a Consensus Definition for COPD Exacerbations. *Chest* **2000**, *117* (5), 398S–401S. https://doi.org/10.1378/chest.117.5_suppl_2.398s.
16. West, J. B. Causes of and Compensations for Hypoxemia and Hypercapnia. *Comprehensive Physiology* **2011**. <https://doi.org/10.1002/cphy.c091007>.
17. Wells, J. M.; Estepar, R. S. J.; McDonald, M.-L. N.; Bhatt, S. P.; Diaz, A. A.; Bailey, W. C.; Jacobson, F. L.; Dransfield, M. T.; Washko, G. R.; Make, B. J.; Casaburi, R.; van Beek, E. J. R.; Hoffman, E. A.; Sciurba, F. C.; Crapo, J. D.; Silverman, E. K.; Hersh, C. P. Clinical, Physiologic, and Radiographic Factors Contributing to Development of Hypoxemia in Moderate to Severe COPD: A Cohort Study. *BMC Pulmonary Medicine* **2016**, *16* (1). <https://doi.org/10.1186/s12890-016-0331-0>.
18. Vold, M. L.; Aasebø, U.; Hjalmarsen, A.; Melbye, H. Predictors of Oxygen Saturation $\leq 95\%$ in a Cross-Sectional Population Based Survey. *Respiratory Medicine* **2012**, *106* (11), 1551–1558. <https://doi.org/10.1016/j.rmed.2012.06.016>.



19. Casanova, C.; Ma Concepción Hernández; Sánchez, A.; García-Talavera, I.; Pablo, J.; Abreu, J.; Jose Manuel Valencia; Aguirre-Jaime, A.; Celli, B. R. Twenty-Four-Hour Ambulatory Oximetry Monitoring in COPD Patients with Moderate Hypoxemia. *PubMed* **2006**, *51* (12), 1416–1423.
20. Pierson, D. J. Pathophysiology and Clinical Effects of Chronic Hypoxia. *Respiratory Care* **2000**, *45* (1), 39–51; discussion 51–53.
21. Salpeter, S. R.; Ormiston, T. M.; Salpeter, E. E. Cardiovascular Effects of β -Agonists in Patients with Asthma and COPD. *Chest* **2004**, *125* (6), 2309–2321.
<https://doi.org/10.1378/chest.125.6.2309>.
22. Chen, W.; Thomas, J.; Sadatsafavi, M.; FitzGerald, J. M. Risk of Cardiovascular Comorbidity in Patients with Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. *The Lancet Respiratory Medicine* **2015**, *3* (8), 631–639.
[https://doi.org/10.1016/s2213-2600\(15\)00241-6](https://doi.org/10.1016/s2213-2600(15)00241-6).
23. Spence, D. P. S.; Graham, D. R.; Ahmed, J.; Rees, K.; Pearson, M. G.; Calverley, P. M. A. Does Cold Air Affect Exercise Capacity and Dyspnea in Stable Chronic Obstructive Pulmonary Disease? *Chest* **1993**, *103* (3), 693–696.
<https://doi.org/10.1378/chest.103.3.693>.
24. Barwood, M. J.; Gibson, O. R.; Gillis, D. J.; Jeffries, O.; Morris, N. B.; Pearce, J.; Ross, M. L.; Stevens, C.; Rinaldi, K.; Kounalakis, S. N.; Riera, F.; Mündel, T.; Waldron, M.; Best, R. Menthol as an Ergogenic Aid for the Tokyo 2021 Olympic Games: An Expert-Led Consensus Statement Using the Modified Delphi Method. *Sports Medicine* **2020**, *50* (10), 1709–1727.
<https://doi.org/10.1007/s40279-020-01313-9>.
25. Kanezaki, M.; Terada, K.; Ebihara, S. Effect of Olfactory Stimulation by L-Menthol on Laboratory-Induced Dyspnea in COPD. *Chest* **2020**, *157* (6), 1455–1465.
<https://doi.org/10.1016/j.chest.2019.12.028>.
26. Nishino, T.; Yugo Tagaito; Sakurai, Y. Nasal Inhalation of L-Menthol Reduces Respiratory Discomfort Associated with Loaded Breathing. *American Journal of Respiratory and Critical Care Medicine* **1997**, *156* (1), 309–313.
<https://doi.org/10.1164/ajrccm.156.1.9609059>.
27. Banzett, R. B.; O'Donnell, C. R.; Guilfoyle, T. E.; Parshall, M. B.; Schwartzstein, R. M.; Meek, P. M.; Gracely, R. H.; Lansing, R. W. Multidimensional Dyspnea Profile: An Instrument for Clinical and Laboratory Research. *European Respiratory Journal* **2015**, *45* (6), 1681–1691.
<https://doi.org/10.1183/09031936.00038914>.
28. Udwadia, F. E.; Udwadia, Z. F.; Kohli, A. F.; Shah, K. *Principles of Respiratory Medicine*; Jaypee Brothers Medical Publishers, 2019.
29. Vestbo, J.; Hurd, S. S.; Agustí, A. G.; Jones, P. W.; Vogelmeier, C.; Anzueto, A.; Barnes, P. J.; Fabbri, L. M.; Martinez, F. J.; Nishimura, M.; Stockley, R. A.; Sin, D. D.; Rodriguez-Roisin, R. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: GOLD Executive Summary. *American journal of respiratory and critical care medicine* **2013**, *187* (4), 347–365.
<https://doi.org/10.1164/rccm.201204-0596PP>.
30. Vogelmeier, C. F.; Criner, G. J.; Martinez, F. J.; Anzueto, A.; Barnes, P. J.; Bourbeau, J.; Celli, B. R.; Chen, R.; Decramer, M.; Fabbri, L. M.; Frith, P.; Halpin, D. M. G.; López Varela, M. V.; Nishimura, M.; Roche, N.; Rodriguez-Roisin, R.; Sin, D. D.; Singh, D.; Stockley, R.; Vestbo, J. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. *American journal of respiratory and critical care medicine* **2017**, *195* (5), 557–582.
<https://doi.org/10.1164/rccm.201701-0218PP>.
31. American Thoracic Society. Dyspnea. *American Journal of Respiratory and Critical Care Medicine* **1999**, *159* (1), 321–340.
<https://doi.org/10.1164/ajrccm.159.1.ats898>.
32. Parshall, M. B.; Schwartzstein, R. M.; Adams, L.; Banzett, R. B.; Manning, H. L.; Bourbeau, J.; Calverley, P. M.; Gift, A. G.; Harver, A.; Lareau, S. C.; Mahler, D. A.; Meek, P. M.; O'Donnell, D. E. An Official American Thoracic Society Statement: Update on the Mechanisms, Assessment, and Management of Dyspnea. *American Journal of Respiratory and Critical Care Medicine* **2012**, *185* (4), 435–452.
<https://doi.org/10.1164/rccm.201111-2042st>.
33. Desbiens, N. A.; Mueller-Rizner, N.; Connors, A. F.; Wenger, N. S. The Relationship of Nausea and Dyspnea to Pain in Seriously Ill



- Patients. *Pain* **1997**, *71* (2), 149–156.
[https://doi.org/10.1016/s0304-3959\(97\)03353-8](https://doi.org/10.1016/s0304-3959(97)03353-8).
34. Grønseth, R.; Vollmer, W. M.; Hardie, J. A.; Ólafsdóttir, I. S.; Lamprecht, B.; Buist, A. S.; Gnatiuc, L.; Gulsvik, A.; Johannessen, A.; Enright, P. Predictors of Dyspnea Prevalence: Results from the BOLD Study. *The European respiratory journal* **2014**, *43* (6), 1610–1620.
<https://doi.org/10.1183/09031936.00036813>.
35. JANSON-BJERKLIE, S.; CARRIERI, V. K.; HUDES, M. The Sensations of Pulmonary Dyspnea. *Nursing Research* **1986**, *35* (3), 154–161. <https://doi.org/10.1097/00006199-198605000-00011>.
36. Kapella, M. C.; Larson, J. L.; Patel, M. K.; Covey, M. K.; Berry, J. K. Subjective Fatigue, Influencing Variables, and Consequences in Chronic Obstructive Pulmonary Disease. *Nursing Research* **2006**, *55* (1), 10–17.
<https://doi.org/10.1097/00006199-200601000-00002>.
37. Stridsman, C.; Skär, L.; Hedman, L.; Rönmark, E.; Lindberg, A. Fatigue Affects Health Status and Predicts Mortality among Subjects with COPD: Report from the Population-Based OLIN COPD Study. *COPD: Journal of Chronic Obstructive Pulmonary Disease* **2014**, *12* (2), 199–206.
<https://doi.org/10.3109/15412555.2014.922176>.
38. Determinants and Impact of Fatigue in Patients with Chronic Obstructive Pulmonary Disease. *Respiratory Medicine* **2009**, *103* (2), 216–223. <https://doi.org/10.1016/j.rmed.2008.09.022>.
39. Wells, J. M.; Estepar, R. S. J.; McDonald, M.-L. N.; Bhatt, S. P.; Diaz, A. A.; Bailey, W. C.; Jacobson, F. L.; Dransfield, M. T.; Washko, G. R.; Make, B. J.; Casaburi, R.; van Beek, E. J. R.; Hoffman, E. A.; Sciurba, F. C.; Crapo, J. D.; Silverman, E. K.; Hersh, C. P. Clinical, Physiologic, and Radiographic Factors Contributing to Development of Hypoxemia in Moderate to Severe COPD: A Cohort Study. *BMC Pulmonary Medicine* **2016**, *16* (1).
<https://doi.org/10.1186/s12890-016-0331-0>.
40. Borg, E.; Borg, G.; Larsson, K.; Letzter, M.; Sundblad, B.-M. . An Index for Breathlessness and Leg Fatigue. *Scandinavian Journal of Medicine & Science in Sports* **2010**, *20* (4), 644–650.
<https://doi.org/10.1111/j.1600-0838.2009.00985>.