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Mechanisms to dyspnoea and dynamic hyperinflation related exercise intolerance in COPD (Review)

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Expiratory flow limitation can develop in parallel with the progression of COPD, and as a consequence, dynamic hyperinflation and lung mechanical abnormalities can develop. Dynamic hyperinflation can cause increased breathlessness and reduction in exercise tolerance. Achievement of critical inspiratory reserve volume is one of the main factors in exercise intolerance. Obesity has specific lung mechanical effects. There is also a difference concerning gender and dyspnoea. Increased nerve activity is characteristic in hyperinflation. Bronchodilator therapy, lung volume reduction surgery, endurance training at submaximal intensity, and heliox or oxygen breathing can decrease the degree of dynamic hyperinflation.

Keywords: COPD, dyspnoea, expiratory flow limitation, dynamic hyperinflation, lung mechanics, exercise tolerance

One of the main symptoms in chronic obstructive pulmonary disease (COPD) is dyspnoea, and initially it is manifested during exercise and later at rest with the progression of the disease. Dyspnoea leads to exercise intolerance in parallel with physical inactivity, and as a consequence, disability may develop (28). The main causes of exercise intolerance may be lung mechanical abnormalities and patient's deconditioning (28).

Dyspnoea is characterised by an increase in the following factors: respiratory work/effort ratio, breathing load, end-expiratory lung volume (EELV) related dynamic hyperinflation, intrinsic positive end-expiratory pressure (PEEP) related elastic effort, and neurological sensation (Fig. 1) (28). Dyspnoea manifestation is often associated with dynamic hyperinflation (DH) in patients with COPD from moderate to severe obstruction (26, 28, 29, 35, 42). The discrepancy between respiratory centre induced respiratory muscle work and muscle load, and capacity related lung volume changes lead to neuromechanical dissociation (Fig. 2). The consequence of this process is the development of dynamic hyperinflation as a cause of chronic and exertional dyspnoea (28).

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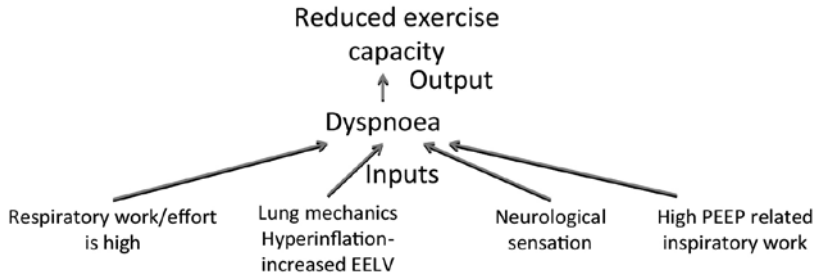

Fig. 1. Schematic representation of contributing factors that worsen dyspnoea

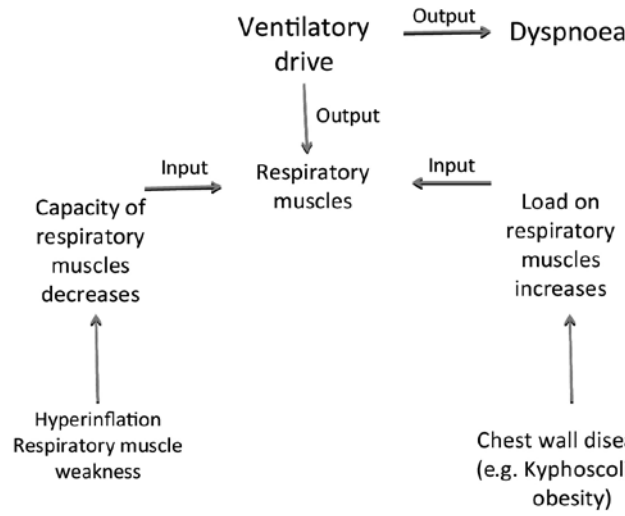

Fig. 2. Schematic representation of inputs to respiratory drive and dyspnoea. Discrepancy between ventilator drive and respiratory muscles' capacity and load related respiratory muscle function

The aim of this review is to understand the mechanisms inducing dyspnoea, lung mechanical changes in COPD and the importance of DH. We will have an overview about the reduction of dynamic hyperinflation by pharmacotherapy, and the importance of complex pulmonary rehabilitation improving the quality of life in COPD, and how it delays dynamic hyperinflation.

Anatomical characteristics in COPD

COPD is a structural and functional disorder of the lungs, which has an effect on lung parenchyma and lung mechanics (2, 5, 21, 41). As a basic feature of emphysema, the alveolar wall can be destroyed and the surface of gas exchange can reduce. Elastic recoil of the lungs can reduce because of destruction in the alveolar attachment and as a consequence static hyperinflation can develop (2, 21, 41). Airway resistance is increased in COPD, and as a consequence, flow limitation can develop (2, 21, 41). Flow limitation is progressive; it has

association with chronic inflammation of the airways in response to noxious particles and gases (2). Flow limitation can be demonstrated by flow-volume curves. Tidal flow-volume curve can achieve the maximum flow-volume curve during exercise showing flow limitation (Fig. 3). Chest wall compartments such as the upper and lower rib cages and abdominal compartments, and rib cage distortion are changing during exercise. These factors have an effect on exercise but with no strong relationship with dyspnoea (5).

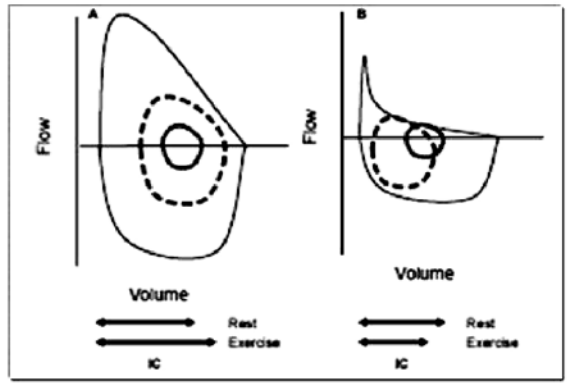

Fig. 3. Maximum and tidal flow-volume curves during exercise with and without flow limitation. The inner dotted line shows flow-volume curves at rest, and the dashed line shows it at maximal exercise. Panel A without and panel B with flow limitation. Flow limitation during exercise in COPD (Adapted from reference 34, reprinted with the permission of Dovepress. Copyright © 2014 Dovepress)
Abbreviations are the following: COPD: chronic obstructive pulmonary disease, IC: inspiratory capacity

Mechanisms to hyperinflation

In hyperinflation, the respiratory system's relaxation volume can move to a higher level because of parenchymal destruction of emphysema, which increases lung compliance (29). In the case of expiratory flow limitation, EELV can also dynamically change and vary with the time constant for emptying (the product of resistance and compliance) of the respiratory system. DH therefore refers to this temporary and variable increase in EELV (28, 29). In flow-limited patients, EELV is a continuous dynamic variable, which depends on expiratory flow limitation and breathing pattern. DH in flow-limited patients is a consequence: as ventilation increases and expiratory duration decreases, there is not enough time to allow EELV to decline to its baseline resting value. Finally, inspiration begins before expiration is complete and DH is the result (28, 29).

In asthma, DH may develop because of active braking by the ribcage muscles during expiration but there is no evidence for the same phenomenon in COPD (29). As a potential mechanism, DH during induced bronchoconstriction may develop asthma as a result of afferent sensory feedback from vagal airway mechanosensors activated by dynamic airway compression during expiration (29). In this situation, mechanosensors can stimulate inspiratory muscle activation before expiration is complete and as a consequent EELV can increase. Induced dynamic airway compression in COPD at rest and during exercise (22, 29) has been shown to consistently have a tachypneic influence on breathing and it can be speculated that airway mechanoreceptor afferent input may similarly influence the control of EELV during exercise (29).

Significant DH has been recorded in the following clinical situations: mechanical ventilation in patients with asthma and COPD, methacholine induced bronchoconstriction in asthma, COPD acute exacerbation, metronome-paced hyperventilation in COPD, and during the increased ventilation of weight bearing or cycle exercise in patients with COPD and cystic fibrosis (29).

Transpulmonary pressure

The pressure difference between lung surface and the entrance of the airways is transpulmonary pressure, which equals the difference between alveolar pressure and the intrapleural pressure in the lungs at a pause of breathing (45).

Since atmospheric pressure is relatively constant, pressure in the lungs must be higher or lower than atmospheric pressure for flowing air between the atmosphere and the alveoli (45). Elastic recoiling of the lungs can generate the pressure needed to flow air. In physiological conditions, the transpulmonary pressure is always positive; intrapleural pressure is always negative and relatively high, while alveolar pressure moves from a slightly positive value to a slightly negative one during breathing (45). At any lung volume, the transpulmonary pressure is equal and opposite of the elastic recoil pressure of the lungs (45).

There is a difference between inhalation and exhalation in transpulmonary pressure vs. volume curve (usually plotted as volume in function of pressure). The lung volume at any given pressure during inhalation is lower than the lung volume at any given pressure during exhalation (45).

Respiratory work

Respiratory work can be generated by the respiratory muscles during inspiration and expiration. Respiratory work needs to be produced because of elastic resistance and flow-resistive forces of the thorax and lungs (24). At rest, the respiratory muscles require about 0.5–1.0 mL of oxygen per ventilation litre. With increasing ventilation, the oxygen cost per unit of ventilation becomes progressively greater. It has been estimated that 10% or more of the total oxygen uptake is needed for respiratory work during heavy exercise (24).

Intensity of dyspnoea

The intensity of dyspnoea depends on the respiratory effort (pleural pressure/maximal inspiratory pressure) and the duration of inspiration. Different ratios can be used to characterise inspiratory effort during exercise. Oesophageal pressure/maximal inspiratory pressure (Peso/Pim) ratio (43), and tidal volume/vital capacity ratio (V_T/VC) as a respiratory neuromechanical index can be used (18, 25). In special cases, gas exchange abnormalities lead to critical arterial hypoxaemia and hypercapnia, which are in a direct or indirect way causing dyspnoea during exercise (28). These factors depend on each other, and a complex integrity to breathing discomfort can develop (28). Mechanical factors, such as acute dynamic hyperinflation has an effect on breathing severity during exercise (28). Studies show that bronchodilator therapy, lung volume reduction surgery, or oxygen breathing reduce hyperinflation and dyspnoea (Fig. 4) (6).

It is difficult to evaluate the potential effect of dynamic hyperinflation on respiratory symptoms, including V_T restriction negative effect, pressure change in the chest and functional weakness of inspiratory muscles (10, 26). Dynamic hyperinflation as a potential dyspnoea

inducing mechanism has an effect on inspiratory load, induction of inspiratory muscle fatigue, chemoreceptor stimulation with carbon-dioxide (CO_2) retention and arterial desaturation (Fig. 5) (26). In previous studies, healthy subjects and interstitial lung disease patients have shown that the limitation of V_T increment has an association with increased respiratory work (effort), which is related to dyspnoea intensity and inspiratory difficulty in COPD (10, 18, 26). The bronchodilator effect on V_T increment and reduction in dyspnoea support the hypothesis that V_T restriction is an important and potential reversible dyspnoea factor (26).

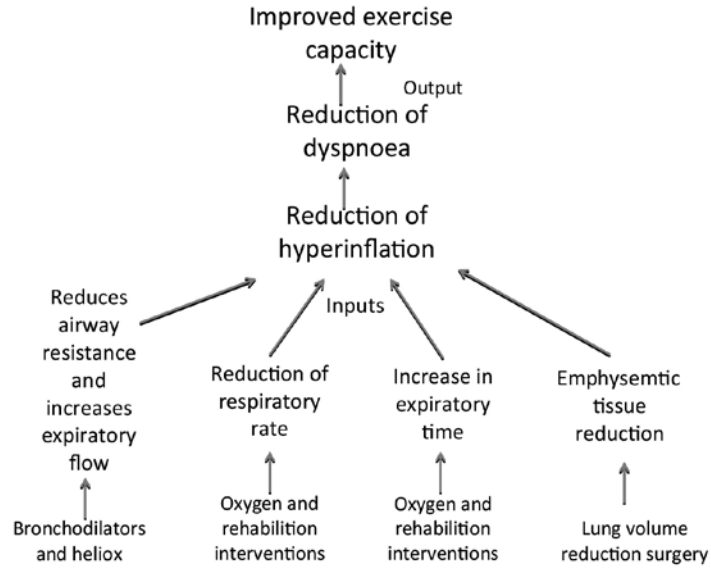

Fig. 4. Schematic representation of different mechanisms to reduce hyperinflation

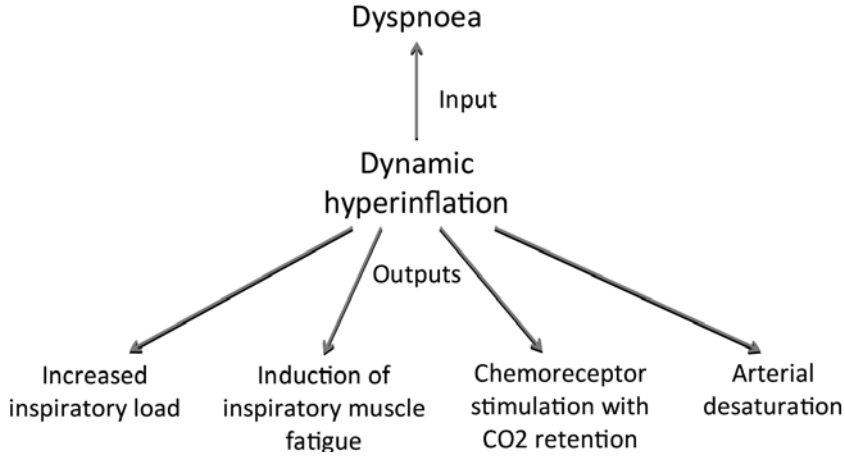

Fig. 5. Pathophysiological consequences of dynamic hyperinflation

Lung mechanical abnormalities

Lung mechanical abnormalities are specific. Irreversible airway obstruction and expiratory flow limitation (EFL) during tidal breathing lead to a swing in intrathoracal gas volume (35). End-expiratory lung volume (EELV) is increasing with the progression of the disease. As flow limitation is achieved, more respiratory work with more respiratory energy is needed (35). Because of the increasing respiratory rate and reduction in exhalation time, lung volumes do not normalize during exercise, and increasing EELV with dynamic hyperinflation can develop (6, 35, 42, 46). These factors significantly increase dyspnoea, and the quality of life worsens (6, 35, 48).

At rest and during exercise, dynamic hyperinflation induces dyspnoea, which may lead to neuromechanical dissociation (36). The favourable effect of bronchodilator treatment in moderate to severe COPD patients reduces chronic and exertion dyspnoea with the reduction of starting EELV and IC increases (36). These factors correlate more strongly with the degree of dyspnoea and exercise tolerance compared to forced expiratory volume in one second (FEV_1) (36).

Critical inspiratory reserve volume and exercise tolerance

The increment of dynamic hyperinflation and decrease in inspiratory reserve volume (IRV = TLC (total lung capacity)-EELV) increase dyspnoea and reduce exercise tolerance in COPD patients (15). Physical activity in patients with COPD decreases with dynamic hyperinflation during exercise. Dynamic hyperinflation worsens dyspnoea on exercise and quality of life (15). As dynamic hyperinflation increases, IRV can fall below a critical level in daily life (7, 15). IRV and the degree of dyspnoea have no linear relationship in patients with moderate to severe COPD. At a certain level of IRV, there is an inflection point, where the dyspnoea significantly increases. This inflection point is 0.3–0.5 litre in IRV, and from this level tidal volume (V_T) cannot further exceed (7, 9). However, achievement of critical V_T and IRV has a significant effect on the intensity of dyspnoea and exercise tolerance independently from the degree of dynamic hyperinflation (10).

O'Donnell et al. have focused on the mechanical effect in relation with critical dyspnoea and IRV in constant work rate test (CWR) (26). The hypothesis has been that in the early phase of exercise, hyperinflation has a favourable effect on respiratory sensation in terms of reducing expiratory flow limitation (27). However, by achieving critical IRV, the intensity of dyspnoea significantly increases with the increasing respiratory effort (Pes/Ptot, V_T/VC) (26). Based on the critical mechanical restriction theory, in hyperinflated patients the main factors are the intensity of dyspnoea, ventilation, breathing pattern, operative lung volumes, Pes-dependent dynamic respiratory mechanics and dyspnoea-IRV inflection point (28).

Difference of lung mechanics during exercise between healthy subjects and COPD patients

Tidal volume in parallel with ventilation is needed to increase during exercise. In healthy subjects, because of absence of flow limitation, end-expiratory lung volume (EELV) can decrease and end-inspiratory lung volume (EILV) can increase, but it does not achieve the critical inspiratory reserve volume (IRV) volume (500 mL) (Fig. 6) (7, 29, 34). In COPD patients, as a consequence of flow limitation, EELV and EILV increase, and IRV value can reduce to a critical interval (< 500 mL) (Fig. 6) (7, 29, 34).

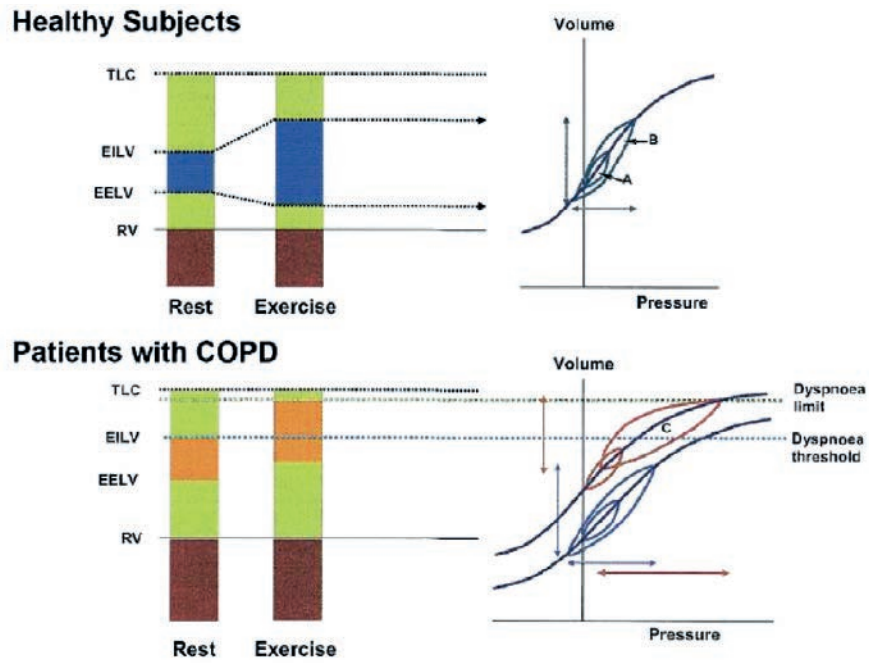

Fig. 6. Operational lung volumes during exercise in healthy subjects and COPD patients. On the compliance curves the small ellipsis (A) represents the volume at rest and the large ellipsis (B) in healthy subjects (upper panel), and the small ellipsis (C) represents the volume at rest and the large ellipsis (D) in patients with COPD. (Adapted from reference 6, reprinted with the permission of the Elsevier. Copyright © 2014 Elsevier) Abbreviations are the following: EELV: end-expiratory lung volume, EILV: end-inspiratory lung volume, IRV: inspiratory reserve volume, TLC: total lung capacity

Obesity and lung mechanics, dynamic hyperinflation

In COPD, especially in the bronchitis phenotype, obesity is an important comorbidity. Obese patients even without an airway disease have restrictive lung disease with the reduction of respiratory system compliance (11, 31). At low static lung volume, an increment in airway resistance and expiratory flow limitation are manifested in obese patients. Otherwise, lower resting and exercise-induced EELV and increased ERV are manifested with increased resting IC in obese patients (11, 29) (Fig. 7). In relation with EELV, a dynamic change in lung volumes leads to natural relaxation volume of the respiratory system, which can correct the negative mechanical effect of obesity. Obesity and COPD have a combined mechanical effect on EELV, but this effect exponentially decreases with BMI increment (11, 31). Obesity in COPD does not have a negative effect on resting IC, symptom-limited peak oxygen uptake (VO_2) and dyspnoea during exercise (31). In a retrospective analysis in COPD, increased BMI does not have a negative effect on resting IC, exercise time in a CWR test, and the degree of dyspnoea during exercise (31).

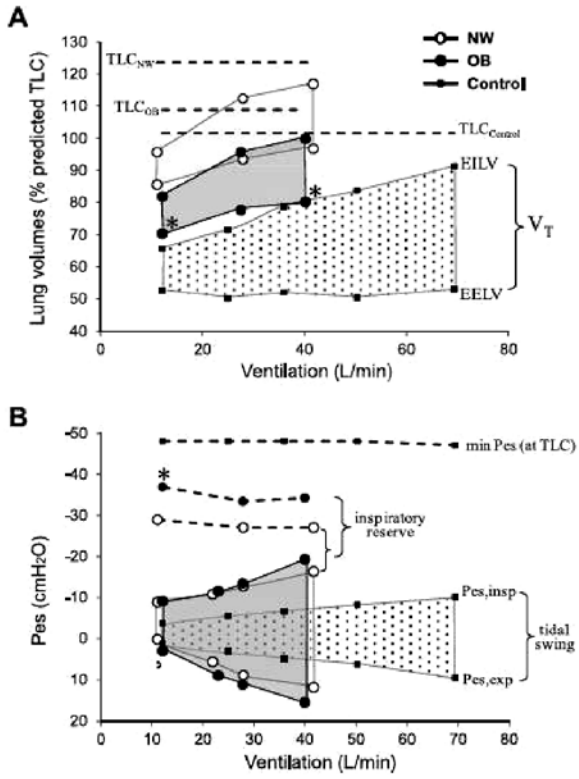

Fig. 7. Lung mechanisms of normal-weight and obese patients with COPD during exercise (Adapted from reference 31, reprinted with the permission of the American Physiological Society. Copyright © 2013 American Physiological Society). Healthy subjects show the lowest (difference between EELV, EILV and TLC is bigger) results, and then it is a bit higher in obese COPD patients, and the highest dynamic hyperinflation can be seen in normal-weight patients with COPD. Abbreviations are the following: NW: normal-weight COPD patient, OB: obese COPD patient, Control: age- and gender-matched healthy control, TLC: total lung capacity, EELV: end-expiratory lung volume, EILV: end-inspiratory lung volume, V_T: tidal volume, Pes: oesophageal pressure, open circle: normal-weight COPD patients, closed circle: obese COPD patient, square: healthy control

The effect of obesity on respiratory muscles/mechanical factors is difficult to predict during exercise, because it depends on the combined effect of many factors (11, 31). It has a potentially negative effect on respiratory muscles with increased elastic load of the respiratory system; it increases metabolic and respiratory load, and increases airway dysfunction and resistance at lower absolute lung volumes (31). As a potential positive effect at lower EELV, the length of the diaphragm can be longer, and because of increased elastic strength, the elastic recoil can improve (11, 31). Ora et al. have shown that there is correlation between increased static elastic strength, reduced EELV, maintained or increased IC, increasing intraabdominal pressure and improving function of the diaphragm in COPD (31). These obesity-dependent physiological differences did not increase in terms of neuromechanical dissociation of the respiratory system and dyspnoea during exercise compared to normal weight COPD patients (31).

Correlation between desaturation during exercise and dynamic hyperinflation

Desaturation during exercise (ED) in COPD can be a predictive factor of mortality (47). The main pathophysiological factors are ventilation-perfusion mismatch and drop of mixed venous oxygen saturation related desaturation during exercise in COPD (47). A higher value of diffusion capacity (DLCO) and resting oxygen saturation mostly do not predict desaturation during exercise. Dynamic hyperinflation has a correlation with lower oxygen and increased exhaled CO_2 content (47). These processes have a correlation with higher ventilation-perfusion mismatch and lower mixed venous oxygen content, and they lead to dynamic hyperinflation related oxygen uptake increment in the respiratory muscles (47).

Inspiratory muscle training and dynamic hyperinflation

Inspiratory muscle training (IMT) is adjuvant therapy in pulmonary rehabilitation, especially in patients with weak respiratory muscles (8, 32). IMT has a positive effect on dyspnoea, but it has a controversial effect on exercise tolerance (8, 32, 37). In an outpatient IMT training study, the capacity of inspiratory muscles, exercise tolerance, dyspnoea and inspiratory fraction ([IF] = IC/ total lung capacity [TLC]) have been measured (8, 32). IMT decreased dynamic hyperinflation, dyspnoea, and exercise tolerance increased (8, 32).

Nerve activity and dynamic hyperinflation in COPD

There is an increased nerve activity at rest in COPD (40). There are several factors in the background of increased nerve activity of the respiratory muscles. These factors involve increased airway resistance, pathological gas exchange, respiratory muscle weakness and high respiratory load. High inspiratory nerve activity, especially in functionally weak inspiratory muscles leads to increased respiratory load (Fig. 8) (24, 40). Work sensation/ effort neurological afferentation includes sensation of the cortical and bulbar motor centres (23, 32), and afferentation of respiratory and skeletal muscles through mechanical and metabolic receptors to the sensory cortex (40).

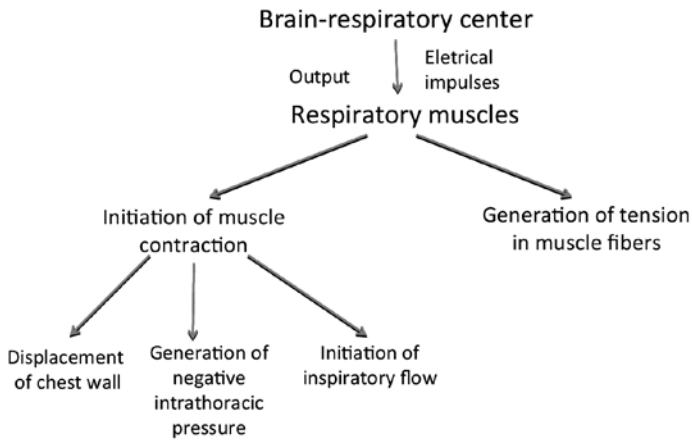

Fig. 8. Relationship between brain respiratory system and respiratory muscles in terms of initiation of muscle contraction and generation of tension in muscle fibres

Dyspnoea in the two genders

Female patients with asthma and COPD perceive more severe dyspnoea at the same ventilatory, exercise and metabolic load (9, 10, 12, 14). In female patients with COPD, other factors than the respiratory ones should be evaluated in the background of dyspnoea (10, 12). In general, the differences between genders at absolute and relative exercise tolerance are based on the different body size (9, 10, 12).

Dynamic airway compression and dynamic hyperinflation

Dynamic airway compression can develop in most of the patients with severe COPD (<40 %pred) during exercise, which can be characterized by flow-volume loops (Fig. 9) (22, 44). In this group, dynamic hyperinflation develops in an earlier phase (22, 44). Patients with dynamic airway compression can achieve higher dyspnoea at a lower ventilation level, lower exercise tolerance and tidal volume (22, 44).

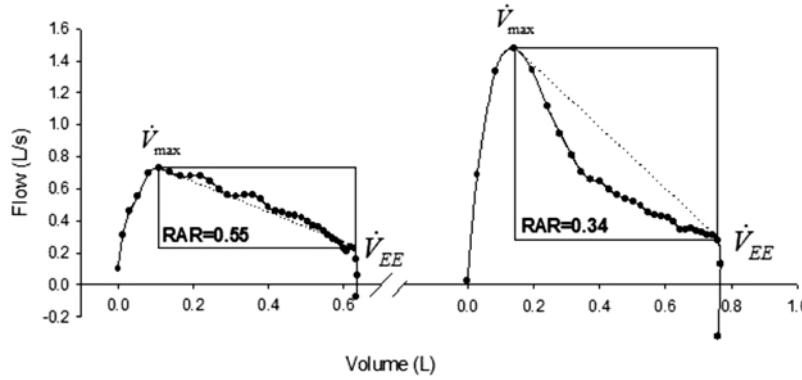

Fig. 9. Expiratory limb of the flow-volume curve of a COPD patient with severe obstruction (FEV_1: 29 %pred) (left side at rest, right side at peak exercise). On the right side of the figure, dynamic airway compression can be detected with a concave shape change manifestation (RAR < 0.5). RAR: rectangular area ratio (area under the curve/ rectangular area). $\dot{V}$ max: maximal flow, $\dot{V}_{EE}$: end-expiratory flow

Physiological mechanisms to reduce dynamic hyperinflation

Activity limitation is multifactorial in COPD; dynamic ventilatory mechanics play an important role. The aim of the therapy is to reduce reversible lung hyperinflation leading to reduction in dyspnoea and improvement in exercise tolerance (1, 28).

Reduction of hyperinflation is the main mechanism of improvement in exercise tolerance and physical activity in COPD. Based on four physiological mechanisms, interventions can improve exercise tolerance in relation with reduction in dynamic hyperinflation (1, 6). An increment of expiratory airflow or reduction in breath rate, and an increase in expiratory time can improve dynamic hyperinflation (1, 6). Bronchodilators and heliox reduce airway resistance and increase expiratory flow speed (Fig. 4) (1, 6). Oxygen supplementation and rehabilitation interventions reduce breath rate and increase expiratory time (Fig. 4) (1, 6, 28). The combination of different interventions leads to further favourable effects (1, 6). Tiotropium and oxygen treatment in combination with rehabilitation have additional favourable effects (6).

High intensity endurance training and dynamic hyperinflation

High intensity endurance training at a certain level of exercise (isotime) reduces dynamic hyperinflation (33). Dynamic training reduces dynamic hyperinflation and improves submaximal exercise tolerance in connection with a reduction in breath rate (33). Lactic acid threshold (LAT) and ventilation response improve (13, 33). These results underline the favourable effect of training on the quality of life of patients in a severe stage as well (13, 33).

Bronchodilators and dynamic hyperinflation

Tiotropium (6), salmeterol (27), indacaterol (4), aclimidium (20), and glycopyrronium (3) have a bronchodilator effect and reduce dynamic hyperinflation (Fig. 4), and improve dyspnoea and exercise tolerance.

Heliox and dynamic hyperinflation

Heliox compared to room air during exercise reduces dynamic hyperinflation at isotime (17). The effect of Heliox on dynamic hyperinflation is parallel with the favourable cardiovascular response and reduction in heart rate (17). Heliox can improve peripherial oxygen delivery in patients with COPD during exercise (Fig. 4) (19).

Oxygen and exercise tolerance

Oxygen in a dose-dependent way (maximal effect at FiO_2: 0.5) improves physical tolerance in connection with the reduction in breathing rate and improvement in dynamic hyperinflation (38). Oxygen can improve exercise tolerance because of the lower ventilatory requirement induced by oxygen supplementation (Fig. 4) (30, 39).

Lung volume reduction surgery

Lung volume reduction surgery reduces dynamic hyperinflation leading to improvement in maximal exercise tolerance and physical activity (Fig. 4) (16, 34). Oxygen pulse increases as a favourable hemodynamic effect (16, 34).

In summary, dynamic hyperinflation worsens the quality of life in COPD patients. Increased symptoms (dyspnoea and reduced physical activity) are manifested with the progression of the disease. Dyspnoea has a connection with the change in lung mechanics and chest pressure. The aim of the therapy is the reduction of dynamic hyperinflation, which can be achieved by bronchodilator therapy, submaximal dynamic training, heliox or oxygen breathing, and lung volume reduction surgery.

Conflict of Interest

The author does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

REFERENCES

1. Almeida P, Rodrigues F: Exercise training modalities and strategies to improve exercise performance in patients with respiratory disease. Rev. Port. Pneumol. 20(1), 36–41 (2014)
2. Baraldo, Turato G, Saetta M: Pathophysiology of the small airways in chronic obstructive pulmonary disease. Respiration 84(2), 89–97 (2012)
3. Beeh KM, Singh D, Di Scala L, Drollmann A: Once-daily NVA237 improves exercise tolerance from the first dose in patients with COPD: the GLOW3 trial. Int. J. Chron. Obstruct. Pulmon. Dis. 7, 503–513 (2012)
4. Beeh KM, Wagner F, Khindri S, Drollmann AF: Effect of indacaterol on dynamic lung hyperinflation and breathlessness in hyperinflated patients with COPD. COPD 8(5), 340–345 (2011)
5. Binazzi B, Lanini B, Gigliotti F, Scano G: Breathing pattern and chest wall kinematics during phonation in chronic obstructive pulmonary disease patients. Respiration 86(6), 462–471 (2013)
6. Casaburi R, Porszasz J: Reduction of hyperinflation by pharmacologic and other interventions. Proc. Am. Thorac. Soc. 3(2), 185–189 (2006)
7. Cooper CB: The connection between chronic obstructive pulmonary disease symptoms and hyperinflation and its impact on exercise and function. Am. J. Med. 119 (10 Suppl 1), 21–31 (2006)
8. Gosselink R: Breathing techniques in patients with chronic obstructive pulmonary disease COPD). Chron. Respir. Dis. 1 (3), 163–172 (2004)
9. Guenette JA, Jensen D, Webb KA, Ofir D, Raghavan N, O'Donnell DE: Sex differences in exertional dypnea in patients with mild COPD: physiological mechanisms. Respir. Physiol. Neurobiol. 177(3), 218–227 (2011)
10. Guenette JA, Webb KA, O'Donnell DE: Does dynamic hyperinflation contribute to dyspnoea during exercise in patients with COPD? Eur. Respir. J. 40(2), 322–329 (2012)
11. Guenette JA, Jensen D, O'Donnell DE: Respiratory function and the obesity paradox. Curr. Opin. Clin. Nutr. Metab. Care 13(6), 618–624 (2010)
12. Harms CA: Does gender affect on pulmonary function and exercise capacity? Respir. Physiol. Neurobiol. 151 (2–3), 124–131 (2006)
13. Hsieh MJ, Lan CC, Chen NH, Huang CC, Wu YK, Cho HY, Tsai YH: Effects of high-intensity exercise training in a pulmonary rehabilitation programme for patients with chronic obstructive pulmonary disease. Respirology 12(3), 381–388 (2007)
14. Kilbride E, McLoughlin P, Gallagher CG, Harty HR: Do gender differences exist in the ventilatory response to progressive exercise in males and females of average fitness? Eur. J. Appl. Physiol. 6, 595–602 (2003)
15. Lahaije AJ, van Helvoort HA, Dekhuijzen PN, Vercoulen JH, Heijdra YF: Resting and ADL-induced dynamic hyperinflation explain physical inactivity in COPD better than FEV1. Respir. Med. 107(6), 834–840 (2013)
16. Lammi MR, Ciccolella D, Marchetti N, Kohler M, Criner GJ: Increased oxygen pulse after lung volume reduction surgery is associated with educed dynamic hyperinflation. Eur. Respir. J. 40(4), 837–843 (2012)
17. Laveneziana P, Valli G, Onorati P, Paoletti P, Ferrazza AM, Palange P: Effect of heliox on heart rate kinetics and dynamic hyperinflation during high-intensity exercise in COPD. Eur. J. Appl. Physiol. 111(2), 225–234 (2012)
18. Laveneziana P, Guenette JA, Webb KA, O'Donnell DE: New physiological insights into dyspnea and exercise intolerance in chronic obstructive pulmonary disease patients. Expert. Rev. Respir. Med. 6(6), 651–662 (2012)
19. Louvaris Z, Zakynthinos S, Aliverti A, Habazettl H, Vasilopoulou M, Andrianopoulos V, Wagner H, Wagner P, Vogiatzis I: Heliox increases quadriceps muscle oxygen delivery during exercise in COPD patients with and without dynamic hyperinflation. J. Appl. Physiol. 113(7), 1012–1023 (2012)
20. Maltais F, Celli B, Casaburi R, Porszasz J, Jarreta D, Seoane B, Caracta C: Aclimidium bromide improves exercise endurance and lung hyperinflation in patients with moderate to severe COPD. Respir. Med. 105(4), 580–587 (2011)
21. Martin C, Frija J, Burgel PR: Dysfunctional lung anatomy and small airways degeneration in COPD. Int. J. Chron. Obstruct. Pulmon. Dis. 8, 7–13 (2013)
22. Ma S, Hecht A, Varga J, Rambod M, Morford S, Goto S, Casaburi R, Porszasz J: Breath-by-breath quantification of progressive airflow limitation during exercise in COPD: a new method. Respir. Med. 104(3), 389–396 (2010)
23. McCloskey DI (1981): Corollary discharges: motor commands and perception. In: Handbook of Physiology, Section 1 the Nervous System, Volume I Cellular Biology of Neurons, Part 2, eds Brookhart JM, Mountcastle VB, Bethesda, American Physiology Society, pp. 1415–1417

24. Nissel O: The respiratory work and pressure during exercise, and their relation to dyspnea. Acta Med. Scan. 166(2), 113–119 (1960)
25. O'Connell JM, Campbell AH: Respiratory mechanics in airways obstruction associated with inspiratory dyspnea. Thorax 31(6), 669–677 (1976)
26. O'Donnell DE, Hamilton AL, Webb KA: Sensory-mechanical relationships during high-intensity, constant-work-rate exercise in COPD. J. Appl. Physiol. 101(4), 1025–1035 (2006)
27. O'Donnell DE, Voduc N, Fitzpatrick M, Webb KA: Effect of salmeterol on the ventilatory response to exercise in chronic obstructive pulmonary disease. Eur. Respir. J. 24(1), 86–94 (2004)
28. O'Donnell DE, Webb KA: Exertional breathlessness in patients with chronic airflow limitation. The role of lung hyperinflation. Am. Rev. Respir. Dis. 148(5), 1351–1357 (1993)
29. O'Donnell DE, Webb KA: The major limitation to exercise performance in COPD is dynamic hyperinflation. J. Appl. Physiol. 105(2), 753–755 (2008)
30. Oliveira MF, Rodrigues MK, Treptow E, Cunha TM, Ferreira EMV, Neder JA: Effects of oxygen supplementation on cerebral oxygenation during exercise in chronic obstructive pulmonary disease patients not entitled to long-term oxygen therapy. Clin. Physiol. Funct. Imaging 32(1), 52–58 (2012)
31. Ora J, Laveneziana P, Wadell K, Preston M, Webb KA, O'Donnell DE: Effect of obesity on respiratory mechanics during rest and exercise in COPD. J. Appl. Physiol. 111(1), 10–19 (2011)
32. Petrovic M, Reiter M, Zipko H, Pohl W, Wanke T: Effects of inspiratory muscle training on dynamic hyperinflation in patients with COPD. Int. J. Chron. Obstruct. Pulmon. Dis. 7, 797–805 (2012)
33. Porszasz J, Emtner M, Goto S, Somfay A, Whipp BJ, Casaburi R: Exercise training decreases ventilatory requirements and exercise-induced hyperinflation at submaximal intensities in patients with COPD. Chest 128(4), 2025–2034 (2005)
34. Puente-Mastu L, Stringer WW: Hyperinflation and its management in COPD. Int. J. Chron. Obstruct. Pulmon. Dis. 1(4), 381–400 (2006)
35. Richter MJ, Voswinkel R, Tiede H, Seeger W, Schulz R, Ghofrani HA, Reichenberger F: [Dynamic hyperinflation in pulmonary arterial hypertension: "hyperinflator" and "non-hyperinflator"]. Pneumologie 67(5), 280–287 (2012)
36. Sheel AW, Romer LM: Ventilation and respiratory mechanics. Compr. Physiol. 2, 1093–1142 (2012)
37. Similowski T, Derenne JP: Inspiratory muscle testing in stable COPD patients. Eur. Respir. J. 7(10), 1871–1876 (1994)
38. Somfay A, Porszasz J, Lee SM, Casaburi R: Dose-response effect of oxygen on hyperinflation and exercise endurance in nonhypoxaemic COPD patients. Eur. Respir. J. 18(1), 77–84 (2001)
39. Somfay A, Porszasz J, Lee SM, Casaburi R: Effect of hyperoxia on gas exchange and lactate kinetics following exercise onset in nonhypoxemic COPD patients. Chest 121(2), 393–400 (2002)
40. Sorli J, Grassino A, Lorange G, Milic-Emili J: Control of breathing in patients with chronic obstructive lung disease. Clin. Sci. Mol. Med. 54(3), 295–304 (1978)
41. Spurzem JR, Rennard SI: Pathogenesis of COPD. Semin. Respir. Crit. Care Med. 26(2), 142–153 (2005)
42. Tantucci C: Expiratory flow limitation definition, mechanisms, methods, and significance. Pulm. Med. 2013, 749860 (2013)
43. Uldry C, Janssens JP, de Muralt B, Fitting JW: Sniff nasal inspiratory pressure in patients with chronic obstructive pulmonary disease. Eur. Respir. J. 10(6), 1292–1296 (1997)
44. Varga J, Shuyi M, Hecht A, Hsia D, Casaburi R, Porszasz J: Detection of dynamic airway compression during exercise in COPD by breath by breath analysis of spontaneous flow-volume lLoops. ERS Supplement: 204s:P1224 (2006)
45. West (2005): Respiratory physiology: the essentials. MD: Lippincott Williams & Wilkins, Hagerstown, pp. 51–60
46. Wilkens H, Weingard B, Lo Mauro A, Schena E, Pedotti A, Sybrecht GW, Aliveri A: Breathing pattern and chest wall volumes during exercise in patients with cystic fibrosis, pulmonary fibrosis and COPD before and after lung transplantation. Thorax 65(9), 808–814 (2010)
47. Zafar MA, Tsuang W, Lach L, Eschenbacher W, Panos RJ: Dynamic hyperinflation correlates with exertional oxygen desaturation in patients with chronic obstructive pulmonary disease. Lung 191(2), 177–182 (2013)
48. Yan S: Sensation of inspiratory difficulty during inspiratory threshold and hyperinflationary loadings. Effect of inspiratory muscle strength. Am. J. Respir. Crit. Care Med. 160(5 Pt 1), 1544–1549 (1999)