Neural Respiratory Drive measurement for COPD assessment and monitoring

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Abstract

Currently there is an unmet need for more objective assessments that could determine COPD severity. Ideally such objective assessments could also anticipate COPD exacerbations in order to decrease the need for repeated hospital admissions. In this review we outline how patients' neural respiratory drive (NRD) may be determined using the electromyography of the diaphragm as an objective measurement of COPD severity. Respiratory muscle NRD is indeed less influenced by patients' voluntary effort limitation than for example when testing for exercise tolerance in which case the patients themselves decide when to stop. Exercise tolerance tests are better correlated with muscle weakness rather than COPD severity per se. NRD would also be less dependent upon patients' subjective perception of the severity of their breathlessness. A key further advantage is that recent studies showed that the diaphragm electromyography measurements using electrodes placed on the skin are correlated with those obtained using specific electrodes, therefore this method is non-invasive and more acceptable for routine clinical practice. Thus, NRD measurements could be used in COPD in a similar way as electrocardiography is used to evaluate and monitor ischemic heart disease. NRD measurements could therefore complement more established instruments such as lung function tests, FEV1, exercise tolerance tests, the BODE index etc. in COPD. This could lead to better COPD management and reduce the acute exacerbations which are amongst the most common causes of repeated hospital admissions and consume significant resources.
Keywords: *COPD, dyspnea, biomarker, exacerbation, exercise, diaphragm, fatigue, respiratory drive*

Rezumat

Măsurarea stimulului respirator central pentru evaluarea și monitorizarea BPOC

La ora actuală există nevoia identificării unor instrumente mai obiective de evaluare a severității BPOC. În mod ideal, acestea ar trebui să anticipeze și exacerbările BPOC, cu scopul de a reduce nevoia internărilor repetate în spital. Acest referat subliniază modul de măsurare a stimulului respirator central cu ajutorul electromiografiei diafragmului, ca un instrument obiectiv de apreciere a severității BPOC. Tehnica este mai puțin influențată de limitarea voluntară a efortului impusă de pacient în comparație cu testarea toleranței la efort – în care pacientul însuși decide asupra sistării efortului. Testele de efort corelează mai bine cu slăbiciunea musculară decât cu severitatea în sine a BPOC. Stimulul respirator central este de asemenea mai puțin dependent de percepția subiectivă a pacientului asupra severității dispneei. Un alt avantaj-cheie demonstrat de studii recente este faptul că electromiografia diafragmului efectuată cu ajutorul electrozilor plasați pe piele se corelează cu măsurătorile obținute utilizând electrozi specifici, așadar metoda este neinvazivă și mai acceptabilă în practica clinică curentă. Măsurarea stimulului respirator central prin această tehnică ar putea fi utilizată la pacienții cu BPOC într-un mod similar folosirii electrocardiografiei pentru evaluarea și urmărirea pacienților cu boală cardiacă ischemică. Măsurarea stimulului respirator central ar putea astfel completa alte instrumente deja folosite în BPOC precum testele funcționale respiratorii, VEMS, testele de efort, indexul BODE etc. Aceasta ar putea duce la un management mai bun al cazurilor de BPOC și la reducerea exacerbărilor care reprezintă una din cele mai frecvente cauze de spitalizare repetată, cu consum important de resurse.
Cuvinte-cheie: *BPOC, dispnee, biomarker, exacerbare, efort, diafragm, oboseală, stimul respirator*

Introduction

Acute exacerbations of COPD have a significant negative impact on patients' quality of life and epidemiological predictions reveal that by 2020 COPD may become the principal cause of death worldwide[1]. Indeed, the prevalence of COPD in the UK is 5.1% of adults aged 18 years or over[2,3] whereas, in China the prevalence defined using the GOLD diagnostic criteria is even higher at 8.2%, possibly as a consequence of one third of the world's smoking population residing in China[4,5].

COPD exacerbations are a frequent cause of emergency admission to hospitals in many countries and entail significant costs, between £810 and £930 million per year in the UK and $29.5 billion in the US[6-8]. There is also an increasing trend in the percentage of patients with COPD being repeatedly admitted to hospitals (31% to 33% over five years)[8]. Indeed, the USA recorded 726,000 emergency admissions and 119,000 deaths from COPD per year[9].

Therefore, enhanced care packages have been created in primary care to optimise COPD follow-up after hospital discharge, with the goal of reducing the need for acute hospital admissions[10,11]. Additionally, early warning scores (EWS) calculating six variables into a composite score, were developed to detect acute physiological deterioration[12,13].

Within this framework, COPD severity can be measured using a variety of methods and scoring systems. Widely used classifications are the GOLD criteria, which uses FEV1, and the BODE index, which in addition to FEV1 uses the MMRC Dyspnea scale, exercise tolerance and body mass index. These measures are however affected by patients' own perception of breathlessness or tiredness, limiting the reliability of these instruments as objective evaluations of COPD severity.

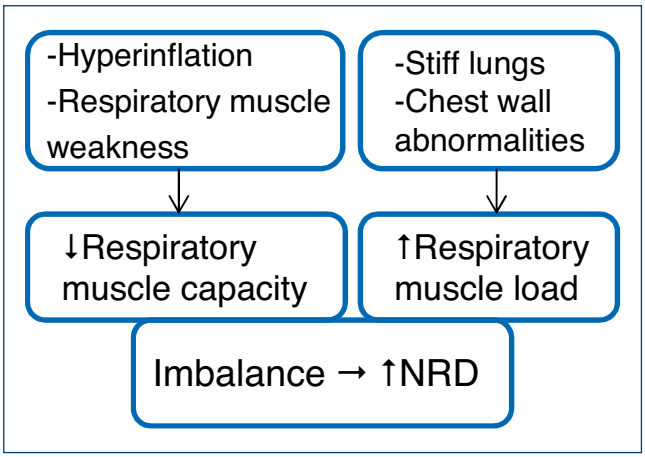

Figure 1. *Relation between respiratory muscle load, respiratory muscle capacity and NRD. Contributing factors that are usually present in COPD are also outlined. Ventilatory capacity is the ability of the respiratory muscles to move air in and out of the lungs and is affected by disorders that hyperinflate the lungs, which stretch these muscles, or by disorders that cause respiratory muscle weakness. Ventilatory load is the load on the respiratory muscles, which may be caused by stiffness of the lungs, increased PEEP or chest wall disorders. An imbalance in capacity and load increases the NRD output of the medullary respiratory centre to the respiratory muscles that can be measured by respiratory muscle electromyography*

Breathlessness and NRD in COPD

COPD is characterised by chronic airway inflammation and lung tissue damage leading to expiratory flow limitation, pulmonary vascular changes and peripheral muscle dysfunction[14,15]. Clinically COPD manifests by fatigue, cough, sputum production and breathlessness, which is defined as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity"[16].

This subjective sensation of breathlessness, reflecting inadequate gas exchange, leads to an increase in NRD that affects the respiratory muscles. Indeed, breathlessness can largely be explained by the increased levels of NRD. The respiratory muscles, which are the pumps driving ventilation, are responsible for generating sufficient pressure changes within the lungs to allow for gas exchange at the alveolar level. There is a crucial balance in respiratory mechanics between load and capacity[17-19]. Disease states that disrupt this balance thus trigger breathlessness and eventually respiratory failure. For example, acute exacerbations of COPD cause a reduction in respiratory muscle capacity and an increase in load as shown in Figure 1. Load increase is indeed a direct consequence of the obstructive nature of COPD because more effort from the respiratory muscles is required to overcome the positive end expiratory pressure (PEEP) that is a direct consequence of increased airway resistance[17,18]. The major site of airway resistance is in this case the small airways, those with a diameter of <2 mm[18].

In this framework, damage to the important elastic recoil function of the lung tissue causes loss of traction forces required to maintain the structural integrity of the airway[15,18]. The direct effect is an increase in functional residual capacity (FRC) i.e. static hyperinflation[17,20]. The increased load and reduced capacity is the physiological mechanism for the development of breathlessness.

Ventilatory load, ventilatory capacity and NRD in COPD

In order to quantify ventilatory load, oesophageal and gastric electrodes may be used to measure transdiaphragmatic pressure changes[20]. The esophageal pressure reflects pleural pressure, whilst the gastric pressure is a reflection of abdominal pressure[21]. During inspiration a rise in gastric pressure and a fall in esophageal pressure illustrate a cumulative rise in transdiaphragmatic pressure[20,21]. This approach allows the assessment of COPD responses to exercising, when large swings in transdiaphragmatic pressure are reported due to the large pressure generation required to overcome the intrinsic PEEP[20]. Ventilatory capacity is determined measuring the maximum inspiratory mouth pressure (PImax) against a closed valve. An alternative method is the sniff maneuver[17].

When the ventilatory load-capacity balance is disrupted, breathlessness ensues. Assessments of the balance between ventilatory load/capacity are difficult to implement into routine clinical practice due to the complexity of such measures, such as placing the electrodes and interpreting their measures. Indeed, obtaining repeated measurements easily is a key requirement if a COPD biomarker is likely to be adapted for wider use in clinical settings. However, the increase in this ratio has been correlated with a rise in NRD[17]. Indeed, load-capacity imbalance increases the output of NRD from the medullary respiratory centre to the respiratory muscles. This is as a result of activation of neural afferents such as pulmonary stretch fibres and intercostal muscle spindles, described by Campbell and Howell (1963) as the "efferent-afferent mismatch"[22]. They hypothesize that the brain expects a certain ventilatory rhythm for a given level of NRD. Stimulation of central and peripheral chemoreceptors by hypoxia and hypercapnia can further increase the sensation of breathlessness.

Electromyography (EMG) is the recording of the electric activity of the muscle, resulting from the membrane depolarization of myocytes that underlies muscle contraction. Stronger muscle contractions involve increasing numbers of motor units and are therefore reflected by higher EMG signals. In this respect the EMG of the diaphragm (EMGdi) is a surrogate measure of NRD.

Jolley et al. (2009) hypothesized that COPD subjects would have a higher EMG diaphragm percent max (EMGdi%max, which represents the diaphragm EMG

activity as percentage of the maximal intensity achievable on the diaphragm EMG) than healthy subjects, and that EMGdi%max would be higher in subjects with the most severe COPD[23]. EMGdi was recorded from the crural diaphragm using a multipair electrode inserted into the esophagus. Subjects were in the seated position and baseline recordings of EMGdi were measured at rest and during maximal inspiration to: i) total lung capacity; ii) maximal static inspiratory effort at FRC against a closed valve; iii) maximal sniff maneuver from FRC[23]. Bilateral phrenic nerve stimulation was performed at 80, 85, 90, 95 and 100% of the maximal stimulator output to determine supra-maximality.

EMGdi was found to be significantly higher in the COPD subjects (27.9 ± 9.9%), compared with healthy controls (11.4 ± 3.4%) matched for age, height and BMI[23]. This may be a result of recruiting a large quantity of motor units within the diaphragm, or due to an increase in the motor unit firing. This is supported by work conducted by De Troyer et al. (1997) and Gandevia et al. (1995)[24,25], showing that 95% of the motor units in the control subjects had a peak discharge frequency between 7 and 14 Hz whereas 79% of the units in the COPD patients had a higher peak discharge frequency greater than 15 Hz, the discharge frequency of all units averaged 10.5± 2.4 Hz in the control subjects, but 17.9 ± 4.3 Hz in the patients ($p < 0.001$). Similarly, Gandevia et al. (1995) showed in seven subjects with moderate to severe COPD that the inspiratory discharge frequencies were greater in COPD subjects than in controls for the parasternal (13.4 versus 10.1 Hz, $p<0.05$) and scalene muscles (11.4 versus 8.5 Hz, $p<0.02$). Collectively the work produced by De Troyer, Gandevia and Jolley indicate that patients with severe COPD have an increased NRD not only for the rib cage inspiratory muscles, but also the diaphragm. Indeed, COPD subjects had a smaller tidal volume as a percentage of their predicted vital capacity per unit EMGdi%max, compared with healthy controls (0.8 ± 0.4 arbitrary units versus 1.4 ± 0.6 arbitrary units). This is a reflection of neuromuscular uncoupling that is correlated with disease severity.

The results of this study support the aim that EMGdi%max is higher in COPD than in healthy controls. Furthermore, the highest levels are present in those with the most severe disease. In particular, careful consideration of the patient population, reflected in the subject demographics and lung function, allow for the translation of these results into clinical medicine.

NRD measurement of exercise tolerance in COPD

When a healthy subject's respiratory system is placed under an increased load and reduced capacity, there is an increase in the NRD up to a point before accessory muscles are recruited. This is a protective mechanism against diaphragm fatigue. In a clinically stable population of COPD patients the clinical syndrome of acute exacerbation can be reproduced by exercise testing. Indeed, Qin et al. (2010) showed that in COPD patients NRD is maximal at the end of exercise and a plateau of EMGdi occurs during exhaustive exercise at constant workload[26].

In order to further bring NRD testing closer to the clinic, Duiverman et al. (2004)[27] tested: i) the reproducibility of this EMG technique between test day one and test day two in both COPD patients and healthy subjects; and ii) the responsiveness (sensitivity to change) of this EMG technique by evaluating and comparing respiratory muscle activity and breathing patterns of COPD patients and healthy subjects during breathing against an increasing inspiratory load. EMG electrodes were positioned as follows: one pair bilaterally at the costal margin in the nipple line; one pair bilaterally on the back at the level of the diaphragm; one pair in the second intercostal spaces, one electrode left and one right, 3 cm parasternal, and bipolar electrodes left and right on the neck over the scalene muscles[27].

The reproducibility between day one and day two was reported in this study as acceptable, with a Pearson's correlation co-efficient of 0.8. Focusing on the responsiveness of the intercostal electrodes, the healthy subjects had a mean activity that increased during breathing against the loads from a factor of 1.9 ± 0.6 arbitrary units ($p<0.01$) at T0; a factor of 2.5 ± 0.9 arbitrary units ($p<0.01$) at T1 and T2 a factor of 2.9 ± 0.9 arbitrary units ($p<0.05$) at T3, compared with load zero. In the COPD patients the activity of the intercostal muscles increased with a factor of 3.0 ± 0.6 arbitrary units ($p<0.01$) at T1, with a factor of 3.3 ±0.8 arbitrary units ($p<0.001$) at T2, and with a factor of 4.3 ± 1.0 arbitrary units ($p<0.001$) at T3, compared with load zero. Log EMG activity ratio values of the intercostal muscles were significantly higher in COPD patients compared with healthy subjects at load one ($p<0.01$). A linear relationship between mean log EMG activity ratio and load, which averages the mean activity ratio of the muscles measured was exponentially related to the inspiratory load.

This study has taken what was known about NRD and the invasive monitoring techniques and provided the basis for non-invasive monitoring of NRD. These results were translated to the application of parasternal EMG measurements in healthy and stable COPD subjects as part of the study by Murphy et al. (2011) who showed that NRD may act as a physiological biomarker for predicting clinical change in patients with acute exacerbations of COPD[28]. The results therefore defined a clinically useful and non-invasive test that could be used to test NRD in COPD.

Conclusions

The emergence of NRD as a COPD biomarker shows a promising tool for predicting patient deterioration and readmission to hospital. Nevertheless, randomized large multicentre trials still need to be conducted, with focus toward measuring the effect of treatments on NRD and the load, capacity and drive balance. ■

References

1. Vestbo J, Hurd SS, Rodriguez-Roisin R, Committee GS. [An overview of Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease (GOLD) (revised 2011)]. *Zhonghua Yi Xue Za Zhi* 2012; 92: 937-8.
2. White P. Prevalence of COPD in primary care: no room for complacency. *Family Practice* 2009; 26: 1-2.
3. Akinbami L, Liu X. Chronic obstructive pulmonary disease among adults aged 18 and over in the United States. In: Brief ND, 1998-2009; 1-8.
4. Zhong N, Wang C, Yao W, et al. Prevalence of Chronic Obstructive Pulmonary Disease in China. *American Journal of Respiratory and Critical Care Medicine* 2007 176: 753-60 .
5. Lin H-H, Murray M, Cohen T, C C, Ezzati M. Effects of smoking and solid-fuel use on COPD, lung cancer, and tuberculosis in China: a time based, multiple risk factor, modelling study. *The Lancet* 2008; 372: 1473-83.
6. National Heart, Lung and Blood Institue. Morbidity and Mortality: 2009. Chartbook of Cardiovascular, Lung and Blood diseases. 2009.
7. NCC-CC. Chronic Obstructive Pulmonary Disease. National clinical guidelines on management of chronic obstructive pulmonary disease in adults in primary and secondary care. *Thorax* 2004; 59 (Suppl1): 1-232.
8. Department of Health. Strategy for services for chronic obstructive pulmonary disease in England. 2010; 12-22.
9. Mannino D, Homa D, Akinbami L, Ford E, Redd S. Chronic obstructive pulmonary disease surveillance - United States 1971-2000. 2002; 1-16.
10. Society BT. Intermediate care - Hospital-at-home in chronic obstructive pulmonary disease: British Thoracic Society guideline. *Thorax* 2007; 62: 200-10.
11. Ram FS, Wedzicha JA, Wright J, Greenstone M. Hospital at home for patients with acute exacerbations of chronic obstructive pulmonary disease: systematic review of evidence. *British Medical Journal* 2004; 329: 315.
12. McGaughey J, Alderdice F, Fowler R, Kapila A, Mayhew A, Moutray M. Outreach and Early Warning Systems (EWS) for the prevention of Intensive Care admission and death of critically ill adult patients on general hospital wards. *Outreach and Early Warning Systems (EWS) for the prevention of Intensive Care admission and death of critically ill adult patients on general hospital wards Cochrane Database of Systematic Reviews* 2007: 1-24.
13. Groarke JD, Gallagher J, Stack J, et al. Use of an admission early warning score to predict patient morbidity and mortality and treatment success. *Emergency Medical Journal* 2008; 25: 803-6.
14. Kim V, Rogers TJ, Criner GJ. New concepts in the pathobiology of chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2008; 5: 478-85.
15. Shapiro SD, Ingenito EP. The pathogenesis of chronic obstructive pulmonary disease: advances in the past 100 years. *American Journal of Respiratory Cellular and Molecular Biology* 2005; 32: 367-72.
16. Dyspnea. Dyspnea. Mechanisms, assessment, and management: a consensus statement. American Thoracic Society. *American Journal of Respiratory and Critical Care Medicine* 1999; 159: 321-40.
17. Moxham J, Jolley C. Breathlessness, fatigue and the respiratory muscles. *Clinical Medicine* 2009; 9: 448-52.
18. Jolley CJ, Moxham J. A physiological model of patient-reported breathlessness during daily activities in COPD. *European Respiratory Revision* 2009; 18: 66-79.
19. Roussos C, Macklem PT. The respiratory muscles. *New England Journal of Medicine* 1982; 307: 786-97.
20. O'Donnell DE. Hyperinflation, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease. *Proceedings of the American Thorac Society* 2006; 3: 180-4.
21. Gea J, Agusti A, Roca J. Pathophysiology of muscle dysfunction in COPD. *Journal of Applied Physiology* 2013; 114: 1222-34.
22. Campbell EJ, Howell JB. The sensation of breathlessness. *British Medical Bulletin* 1963; 19: 36-40.
23. Jolley CJ, Luo YM, Steier J, et al. Neural respiratory drive in healthy subjects and in COPD. *The European Respiratory Journal* 2009; 33: 289-97.
24. De Troyer A, Leeper JB, McKenzie DK, Gandevia SC. Neural drive to the diaphragm in patients with severe COPD. *American Journal of Respiratory and Critical Care Medicine* 1997; 155: 1335-40.
25. Gandevia SC, Leeper JB, McKenzie DK, De Troyer A. Discharge frequencies of parasternal intercostal and scalene motor units during breathing in normal and COPD subjects. *American Journal of Respiratory and Critical Care Medicine* 1996; 153: 622-8.
26. Qin YY, Steier J, Jolley C, Moxham J, Zhong NS, Luo YM. Efficiency of neural drive during exercise in patients with COPD and healthy subjects. *Chest* 2010; 138: 1309-15.
27. Duiverman ML, van Eykern LA, Vennik PW, Koeter GH, Maarsingh EJ, Wijkstra PJ. Reproducibility and responsiveness of a noninvasive EMG technique of the respiratory muscles in COPD patients and in healthy subjects. *Journal of Applied Physiology* 2004; 96: 1723-9.
28. Murphy PB, Kumar A, Reilly C, et al. Neural respiratory drive as a physiological biomarker to monitor change during acute exacerbations of COPD. *Thorax* 2011; 66: 602-8.

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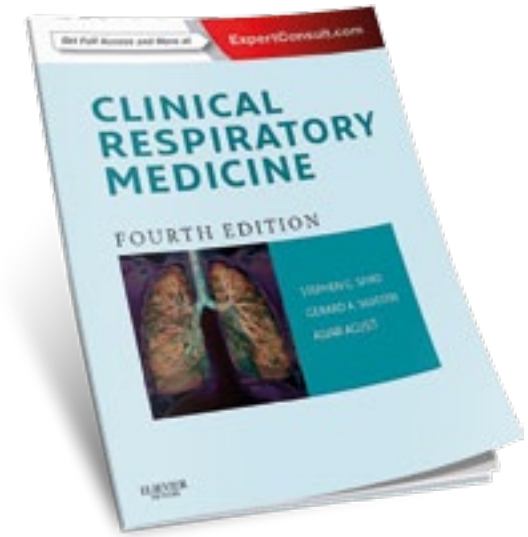

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