

Differential Mechanisms of Dyspnea Relief in Advanced COPD: Opiates vs. Bronchodilators

BACKGROUND & RATIONALE

Chronic obstructive pulmonary disease (COPD) is a common respiratory illness which afflicts almost 10% of Canadians over 40 years of age (1,2). COPD sufferers report poor perceived quality of life and often must endure progressive physiological impairment, increasing morbidity and reduced survival. Activity-related breathlessness (dyspnea) is the dominant symptom and persists despite optimal medical care in as many as 50% of patients with advanced COPD (3). Thus, for many patients, effective relief of dyspnea remains an elusive goal and is a major challenge for caregivers. *Meaningful palliation of this symptom awaits a better understanding of its neurophysiological origins - the main focus of the proposed application.*

The physiology of dyspnea: Dyspnea is defined as “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity” (4). Current constructs of the neurobiology of dyspnea have arisen from animal studies that have provided a plausible neuro-anatomical substrate for respiratory sensation, and from human studies that have measured sensory responses to graded external mechanical and chemical loading in the laboratory setting (5-19). More recently, clinical studies have focused on physiological mechanisms of dyspnea provoked by standardized stimuli (e.g., exercise) in specific patient populations (20,21). A consistent observation has been that dyspnea arises during exercise in COPD when there is mismatch between ventilatory demand (largely dictated by chemical stimuli) and the capacity to respond to that demand (dictated by mechanical/muscular factors) (21,22). In line with this observation, dyspnea ratings during exercise in health and COPD have been shown to correlate strongly with indices such as ventilation relative to maximal ventilatory capacity (V_E/MVC) and contractile muscular effort (esophageal pressure relative to maximum ($P_{es}/P_{es,max}$)) (20-22).

Broadly speaking, these consistent physiological associations support the notion that dyspnea rises as a function of the amplitude of motor command output (and central corollary discharge) from bulbo-pontine and cortical centers in the brain to the active respiratory muscles (23-26) [Appendix 1]. There is some evidence that efferent central inspiratory neural drive (relative to maximum) is more important than afferent inputs from peripheral respiratory (chest wall and muscle) mechanoreceptors in modulating perceived dyspnea (27,28). *While these past studies provide insight into the origins of sensory intensity of respiratory discomfort they do not easily explain differences in the quality of dyspnea between healthy individuals and those with COPD.*

Mechanisms of increased dyspnea intensity: A major limitation in the study of dyspnea is our inability to directly measure central inspiratory neural drive. Surrogate indices such as ventilatory output (V_E/MVC) and contractile effort are dampened by prevailing mechanical constraints and likely underestimate true inspiratory neural drive (29). Recently, diaphragmatic electromyography (EMGdi) has been proposed as an indirect method of measuring the fractional inspiratory neural drive to the crural diaphragm, i.e., inspiratory EMGdi as a fraction of its maximum ($EMGdi/EMGdi,max$) (30-32). Dyspnea intensity ratings during exercise in healthy individuals and those with COPD rise linearly with $EMGdi/EMGdi,max$ (33-35) [Appendix 2]. The higher dyspnea ratings for a given V_E during exercise in COPD compared with healthy subjects is explained by the relatively higher $EMGdi/EMGdi,max$. This in turn reflects the combined effects of increased pulmonary gas exchange abnormalities (high physiological deadspace) and greater intrinsic mechanical loading and functional weakness of the inspiratory muscles. Furthermore, we have shown that the relationship between dyspnea intensity and $EMGdi/EMGdi,max$ is unaffected by differences in static mechanics, respiratory muscle strength and the activity pattern of various inspiratory and expiratory muscles supporting ventilation during exercise (35,36) [Appendix 2]. Collectively, these studies support the long held contention that dyspnea intensity

during activity is closely linked to the magnitude of descending motor command output to the inspiratory muscles. Accordingly, several studies have postulated, based on indirect evidence (breathing pattern and V_E), that reduced inspiratory neural drive is one potential mechanism by which a number of therapeutic interventions reduce dyspnea intensity in COPD (37-42). However, the interpretation of these studies remains conjectural as they have not formally examined relationships between multi-component dyspnea and the integrated neuromechanical responses of the respiratory system to exercise. ***Therefore, the current study will be the first to comprehensively study in a novel manner the interaction between the sensory and neuromechanical effects of one such treatment (i.e., opiate medication), which putatively diminishes inspiratory neural drive during exercise in COPD.***

Quality of dyspnea: It is postulated that the intensity (strength) and quality (how it feels) of respiratory discomfort have different neuro-physiological underpinnings (4). The quality of dyspnea at the limits of tolerance is different in patients with COPD and in health despite similar intensity ratings (22,35). Thus, healthy individuals commonly select *work/effort* descriptors (“breathing requires more effort or work”) as being most representative of their experience while patients with COPD additionally select descriptors alluding to *inspiratory difficulty* and *unsatisfied inspiration* (“cannot get enough air in”). This latter descriptor is perceived as unpleasant and is rarely selected in health, even at high exercise intensities. During exercise in COPD there is an evolution of respiratory sensations from dominant increased *work/effort* early in exercise to *unsatisfied inspiration* later in exercise when tidal volume (V_T) reaches its plateau – a point corresponding to the attainment of a minimal inspiratory reserve volume (IRV) of $\sim 0.5L$ (43). In other words, the point where V_T becomes positioned on the upper non-compliant reaches of the respiratory system’s sigmoidal pressure-volume relation where the inspiratory muscles are burdened with increased elastic work. The V_T plateau marks the onset of a widening disparity between increasing inspiratory neural drive (and central corollary discharge) often amplified by metabolic acidosis and/or hypoxemia and the blunted, mechanically constrained V_T response. This disparity has been called *neuromechanical dissociation*. There is an abundance of mechanoreceptors in the airways, lungs, chest wall and respiratory muscles that can convey precise afferent feedback information about the dynamic status of the breathing apparatus and the appropriateness of its response to descending inspiratory neural drive via central integration of efferent-afferent signals [Appendix 1]. Bronchodilator therapy, which increases resting inspiratory capacity (IC) by reducing lung hyperinflation, delays the onset of critical mechanical constraints (i.e., the minimal IRV) (44,45). We have speculated that the improved ratio of respired effort to V_T ($P_{es}/P_{es,max}:V_T/VC_{predicted}$) – a crude index of neuromechanical dissociation – may explain the reduced selection frequency of *unsatisfied inspiration* after a bronchodilator (44,45). ***The current study will extend the previous work using more sophisticated evaluative methods to determine the mechanisms of dyspnea relief following bronchodilator treatment. Specifically, we will examine the inter-relationships between dyspnea intensity and quality, inspiratory neural drive, dynamic respiratory mechanics and muscle function and how these are altered by bronchodilators.***

Comparing mechanisms of dyspnea relief during opiate (with oxygen) and bronchodilator therapy: We hope to gain new insights into the mechanisms of dyspnea in COPD by selectively manipulating inspiratory neural drive (nebulized opiates) and abnormal respiratory mechanics (nebulized bronchodilators) within the same individuals. In a preliminary study, we established that relief of exertional dyspnea in patients with COPD following inhaled fentanyl – a lipophilic, μ -receptor opioid antagonist – was associated with reduced V_E (37). Thus, inhaled fentanyl did not change the slope of the dyspnea/ V_E relation: the reduction in dyspnea at a given work rate mainly reflects the reduction in V_E and breathing frequency [Appendix 3]. This suggests that reduction in inspiratory neural drive is potentially the key mechanism, particularly since respiratory mechanics were essentially unaltered by

this treatment. By contrast, reduced exertional dyspnea following inhaled bronchodilators in COPD was mainly related to improved mechanics (i.e., increased IC, V_T , and inspiratory reserve volume (IRV); reduced $P_{es}/P_{es,max}:V_T/VC_{predicted}$) as V_E was unchanged or increased (40,44-46). In other words, the dyspnea/ V_E slope was reduced after bronchodilator: improvement in dyspnea at a given V_E mainly reflected the improved mechanics [Appendix 3].

The contrasting physiological effects of these two interventions present us with a unique opportunity to probe the origins of dyspnea in COPD and for the first time, to determine the role of inspiratory neural drive. Based on our recent studies (35,36), we postulate that regardless of the intervention, the key relationship between EMGdi/EMGdi,max and dyspnea intensity will remain unaltered. It follows that with both interventions, dyspnea intensity ratings will be reduced in proportion to the reduced EMGdi/EMGdi,max, albeit through different mechanisms: with opiates, direct central inhibitory effects; with bronchodilators, improved respiratory mechanics/muscle function which necessitate lower inspiratory neural drive for a given V_E . Peculiar to bronchodilators, the improved mechanics will mean an improved ratio of inspiratory neural drive to ventilation and associated reduced *unsatisfied inspiration*.

Studies were done previously on dyspnea relieving interventions in COPD such as the use of bronchodilator therapy and oxygen, both singly and in combination. In a previous study utilizing combined bronchodilator and oxygen therapy, we established that there was reduced hyperinflation (using bronchodilators) and reduced ventilatory drive (using oxygen) in normoxic COPD patients (40). There is minimal information available on the effects of using inhaled fentanyl and oxygen interventions combination on dyspnea in COPD. This would be the first study to demonstrate the physiological effects of inhaled fentanyl combined with oxygen therapy on dyspnea in COPD.

OBJECTIVE: To compare the effects of inhaled opiate (with added oxygen) and bronchodilator treatments on the intensity of dyspnea, electromyographic estimates of inspiratory neural drive and respiratory mechanics and their interactions during a standardized exercise test using a randomized, controlled, crossover design in patients with COPD.

HYPOTHESIS: The mechanisms of dyspnea relief during opiate and bronchodilator treatments will be different. With both inhaled opiate and bronchodilator, inspiratory neural drive and dyspnea intensity will diminish in tandem. Additionally, and in contrast to the effect of opiates, improvement in respiratory mechanics with inhaled bronchodilators will reduce neuromechanical dissociation and the attendant perceived *unsatisfied inspiration*.

METHODS

Subjects: Subjects will include 17 clinically stable patients with moderate-to-severe COPD recruited from: a database of COPD volunteers at the *Respiratory Investigation Unit*; respiratory outpatient clinics at Hotel Dieu Hospital; notices posted in community health care facilities; and advertisements. **Inclusion Criteria:** 1) post-bronchodilator forced expiratory volume in 1 sec (FEV_1) 30-79% predicted and $FEV_1/\text{forced vital capacity (FVC)} < 70\%$; 2) clinically stable as defined by no changes in medication dosage or frequency of administration with no exacerbations or hospital admissions in the preceding 6 weeks; 3) male or female ≥ 40 yrs of age; 4) cigarette smoking history ≥ 20 pack-years; 5) moderate-to-severe chronic activity-related dyspnea as defined by a modified MRC dyspnea scale ≥ 2 , COPD Assessment Test score ≥ 10 or Baseline Dyspnea Index focal score ≤ 6 (47-49); 6) ability to perform all study procedures and provide/sign informed consent. **Exclusion Criteria:** 1) women of childbearing age who are pregnant or trying to become pregnant; 2) diffusing capacity of the lung for carbon monoxide (D_LCO) value of $< 40\%$ predicted; 3) active cardiopulmonary disease other than COPD that could contribute to dyspnea and exercise limitation; 4) history/clinical evidence of asthma, atopy and/or nasal

polyps; 5) history of hypercapnic respiratory failure or a clinical diagnosis of sleep disordered breathing; 6) history of allergy or adverse response to fentanyl; 7) important contraindications to clinical exercise testing, including inability to exercise because of neuromuscular or musculoskeletal disease(s); 8) use of daytime oxygen or exercise-induced O₂ desaturation to < 80% on room air; 9) body mass index (BMI) <18.5 or ≥35.0 kg/m²; 10) use of antidepressant drugs (i.e., monoamine oxidase inhibitors, serotonin reuptake inhibitors) in previous 2 weeks; 11) use of opioid drugs (e.g., morphine, fentanyl, oxycodone, codeine, *etc.*) in the previous 4 weeks.

Study design: This will be a single-centre, randomized, double-blind, 2-treatment crossover study evaluating the differential effects of nebulized fentanyl citrate (100µg) and nebulized bronchodilator (0.5mg ipratropium bromide + 2.5mg salbutamol) on exertional dyspnea and physiological responses to a standardized exercise task. After giving written informed consent, participants will complete 5 visits, each conducted in the morning 2-7 days apart [Appendix 4]. **Visit 1 (screening):** medical history, symptom evaluation, complete pulmonary function testing, a symptom-limited incremental exercise test to determine maximal work rate (W_{max}), and familiarization to a new standardized exercise task (4-min cycle exercise test). **Visits 2 & 3 (run-in):** repeatability of the 4-min cycle exercise test. **Visits 4 and 5 (treatment):** pre-drug pulmonary function tests (spirometry, plethysmography) and a 4-min cycle exercise test while breathing a gas mixture with a constant fraction of 21% oxygen (room air = 21% FiO₂); nebulized of either fentanyl or bronchodilator; 30-min post-drug, subjects will perform post-drug pulmonary function tests and a 4-min cycle exercise test while breathing a gas mixture with a constant fraction of 30% oxygen (30% FiO₂) after fentanyl and 21% oxygen (21% FiO₂) after bronchodilator. Exercise tests at Visits 4 and 5 will include detailed measurements of dyspnea (intensity, quality, affective dimensions), EMGdi and pressure-derived respiratory mechanical measurements. Vital signs and systemic side-effects will be monitored. Regularly used inhaled corticosteroids will be permitted as usual throughout the study. Subjects will adhere to the standard withdrawal of bronchodilators prior to each visit: short-acting β₂-agonists, short-acting anticholinergics, long-acting β₂-agonists and long-acting anticholinergics will be withdrawn 6, 12, 24 and 24 hours, respectively. Subjects will avoid caffeine, heavy meals, alcohol and major physical exertion prior to visits. Although inhalation of fentanyl citrate has not been associated with significant adverse symptoms or side-effects there is always a possibility that study participants could experience certain side-effects such as drowsiness, sedation and dizziness. As such, participants will be required to have someone accompany them home after their fourth and fifth study visit. If someone is not available to drive them on those days they will be required to take a taxi to and from the lab.

Study medications, randomization & blinding: Treatment will consist of a single dose of a 5 ml solution containing either: 100µg of fentanyl citrate (20 µg/ml) or a bronchodilator (Combivent: 0.5 mg ipratropium bromide + 2.5 mg salbutamol) administered by means of a jet nebuliser (Parimaster compressor with Pari LC Jet+ nebuliser; PARI Respiratory Equipment Inc., Richmond, VA, USA) with subjects breathing spontaneously for 15-min via facemask. The order of treatment (fentanyl, bronchodilator) given at Visits 4 and 5 will be randomized. Randomization and dispensing of study drug will be performed by the Investigational Drug Service (IDS; Pharmacy Services, Kingston General Hospital), an unblinded third party not affiliated with patient recruitment or data collection/analysis. Study medication will be supplied by the IDS. Unblinding will be permitted in response to a serious adverse event. The 100µg dose of inhaled fentanyl citrate was selected because: 1) in previous studies, 25µg and 50µg doses had either no effect or improvements of small magnitude (37,50); 2) based on pharmacokinetic studies (51), this dose should not result in any significant absorption into the systemic circulation, which in turn should not produce any significant side-effects; 3) we reasoned that the 25µg and 50µg doses were too small to be effective in patients with significant ventilation-perfusion

abnormalities; 4) most randomized controlled trials of inhaled morphine in cancer patients have used 5mg nebulized doses, equivalent to 50µg of nebulized fentanyl citrate, with only small or inconsistent effects (52). Studies to date have shown inhaled fentanyl to be well tolerated and respiratory depression (CO₂ retention) has not been described at expected plasma levels (2-3µg/kg) (53). Based on our preliminary study, we expect ventilation to fall by 2-4L/min with inhaled fentanyl (37).

Procedures

Pulmonary function testing: Spirometry, body plethysmography, diffusing capacity of the lung for carbon dioxide (D_LCO), maximum inspiratory/expiratory mouth pressures and impulse oscillometry (IOS) will be performed according to recommended techniques using automated equipment (Vmax 229d, Autobox V62j and MasterScreen IOS; SensorMedics, Yorba Linda, CA) (54-59). Measurements will be expressed as % of predicted normal values (60-64).

Cardiopulmonary exercise testing (CPET): Exercise tests will be conducted on an electronically-braked cycle ergometer (Ergometrics 800S; SensorMedics) using a SensorMedics Vmax229d system as previously described (34-36). Incremental CPET will consist of steady-state rest followed by 1 minute of warm-up of unloaded pedalling then 10 watt increases in work rate every minute to the point of symptom-limitation [Appendix 5]. Maximal work rate (W_{max}) will be defined as the highest work rate the subject can maintain for at least 30 seconds. Constant-load tests will consist of steady-state rest, 1 minute of warm-up of unloaded pedalling and then an immediate stepwise increase work rate to 75% which will be maintained for 4 minutes (see below). Measurements will include: standard cardiorespiratory and breathing pattern parameters collected on a breath-by-breath basis and compared with predicted values based on age and height (65); oxygen saturation by pulse oximetry; heart rate by 12-lead ECG; blood pressure by auscultation; operating lung volumes derived from IC maneuvers (66,67); EMGdi-derived measures of inspiratory neural drive to the diaphragm; the intensity of perceived leg discomfort; and exertional dyspnea intensity, quality and unpleasantness. Three main time points will also be evaluated: *rest* will be defined as the steady-state period after at least 3 minutes of breathing on the mouthpiece before exercise starts (cardiopulmonary parameters will be averaged over the last 30-sec of this period and resting ICs will be collected while breathing on the same circuit immediately after completion of the quiet breathing period); *isotime* will be defined as the last 30-sec increment of each minute (i.e., 1-min, 2-min, 3-min) during the 4-min exercise tests, and; *end-exercise* will be defined as the last 30-sec of loaded pedaling (i.e., 4-min).

Adjustment of work rate for 4-min cycle tests. The work rate during the constant-load test will be adjusted to the highest work rate that can be sustained for the entire 4 minutes; the objective is to induce a level of dyspnea (a modified Borg rating ≥ 3) that is sufficiently high to be amenable to therapy. After completion of the incremental test and an adequate rest period at Visit 1, a 4-minute cycle test at 75%W_{max} will be conducted. If the subject can complete 4 minutes and reaches a dyspnea intensity ≥ 3 Borg units, then these work rate settings will be used for all subsequent cycle tests. If the subject cannot complete 4-minutes, then a lower work-rate (60%) will be tested. If the subject completes the 4-minutes but does not reach a high enough dyspnea rating, then a higher work-rate (90%) will be tested. At run-in Visit 2, further refinement of work rate will be conducted if required. After final selection of work rate to use for 4-min tests, repeatability of tests conducted at Visits 2 and 3 using the final selection of work rate will be evaluated by comparing end-exercise dyspnea intensity ratings and standard cardiopulmonary measurements.

Symptom evaluation. Dyspnea (respiratory discomfort) will be defined as the “sensation of breathing discomfort” and leg discomfort as “the sensation of leg discomfort experienced during pedalling.” The intensity (strength) of sensations will be rated at rest and during exercise using the modified 10-point Borg scale (68). We have recently provided validation for the novel use of the same

scale for measuring the intensity of several descriptive phrases related to specific qualities of dyspnea (e.g., effort, unsatisfied inspiration) and the affective dimension (e.g., unpleasantness) of dyspnea (37,69,70). This will allow us to assess which component(s) of perceived dyspnea is modified by the active intervention. Upon exercise cessation, subjects will be asked to verbalize their main reason for stopping exercise, i.e., breathing discomfort, leg discomfort, their combination or some other reason. Qualitative descriptors of respiratory discomfort at end-exercise will be collected by questionnaire (19).

Respiratory pressures and diaphragm electromyography (EMGdi). An esophageal electrode-balloon catheter will be inserted nasally and positioned as previously described (30,71). EMGdi will be recorded continuously using an esophageal electrode catheter consisting of 5 electrode pairs at rest and during exercise and analyzed as previously described (34-36). The raw EMGdi signal will be sampled at 2000 Hz (PowerLab, model ML880; ADInstruments, Castle Hill, NSW, Australia), band-pass filtered between 20-1000 Hz (Bioamplifier model RA-8; Guanzhou Yinghui Medical Equipment Co. Ltd, Guangzhou, China) and converted to a root mean square (RMS) using computer software (Chart v5.4, ADInstruments). For each breath, the data from the electrode pair with the largest value from the five electrode pairs will be used for analysis. Maximal EMGdi (EMGdi,max) will be determined from IC maneuvers (72). EMGdi/EMGdi,max will be used as an index of the inspiratory neural drive to the crural diaphragm (30-33). Esophageal (Pes) and gastric pressures (Pga) will be recorded continuously at a rate of 200 Hz (PowerLab); transdiaphragmatic pressure (Pdi) will be recorded as the difference between Pga and Pes signals. The continuous flow signal from the Vmax229d system will be input into the PowerLab system for offline analysis. Pre- and post-exercise inspiratory sniffs will be performed to obtain maximum Pes (Pes,sn) and Pdi (Pdi,sn). IC maneuvers at rest and throughout exercise will be used to obtain dynamic peak inspiratory Pes (Pes,IC) and Pdi (Pdi,IC). Pre- and post-exercise FVC maneuvers will also be performed to obtain dynamic peak expiratory Pes (Pes,FVC). Respiratory mechanics will be analyzed as previously described (34-36).

Statistical analysis: A sample size of 17 will provide at least 80% power to detect a clinically significant treatment difference of 1 Borg unit in dyspnea intensity at a standardized time during constant work-rate exercise (i.e., at the end of the 4-min exercise test). This sample size estimation is based on the following assumptions: a standard deviation of 1.35 Borg units for the difference between values in a two-treatment crossover study [Appendix 3] (37,40), $\alpha=0.05$, $\beta=0.8$, and a two-tailed test of significance. A $p<0.05$ significance level will be used for all statistical analyses.

Paired *t*-tests with appropriate Bonferroni adjustments for multiple comparisons will be used to compare treatment responses, i.e., post-dose responses to fentanyl citrate versus bronchodilator. Comparisons will be made for: 1) resting pulmonary function; 2) cardiorespiratory (e.g., V_E , V_T , breathing frequency, HR, etc.), respiratory mechanical (e.g., IC, inspiratory reserve volume (IRV)), metabolic and gas exchange (e.g., VO_2 , carbon dioxide output (VCO_2), end-tidal CO_2 ($P_{ET}CO_2$), SpO_2), and perceptual (e.g., intensity of dyspnea and leg discomfort) responses measured at rest, isotime and end-exercise; 3) Pes, Pga and Pdi-derived measurements of respiratory mechanics and muscle recruitment patterns; 4) EMGdi-derived indices of inspiratory neural drive (e.g., EMGdi/EMGdi,max). Descriptors of dyspnea at end-exercise and reasons for stopping exercise will be analyzed as frequency statistics and compared between-groups and between-treatments using Fisher's exact test.

To identify contributors to exertional dyspnea intensity (and its qualitative and affective dimensions), Pearson correlations will be used to establish associations between intra-subject treatment differences (i.e., post- minus pre-treatment) in isotime (4-min) measurements of exertional dyspnea intensity and relevant independent variables which will include: concurrent differences in cardiorespiratory and dynamic respiratory mechanical measurements at isotime during exercise; differences in resting lung function measurements, and; various baseline characteristics (possible

covariates). A multivariable linear regression model will be used to further evaluate the relationship between dyspnea intensity and any significant variables: treatment will be included as a categorical effect, an interaction term will be used to determine whether the relationship was similar across treatments (independent variable*treatment), and subjects will be treated as random effects to account for serial measurements (subject nested within treatment).

ANTICIPATED RESULTS & SIGNIFICANCE OF THE STUDY: We anticipate that the results will show that opiates and bronchodilators ameliorate dyspnea in COPD through different mechanisms. By comparing the mechanisms of dyspnea relief during distinctly different interventions, we will greatly advance our understanding of the neurophysiology of dyspnea causation. Our results will provide a solid physiological rationale for combining dyspnea-relieving medications with different modes of action in order to achieve additive or synergistic effects. Uncovering the mechanisms of action of inhaled fentanyl will set the stage for subsequent clinical trials to determine its efficacy for the management of breakthrough or intermittent dyspnea in patients with chronic lung diseases. We do not expect any significant barriers; we have access to a large group of patient volunteers and have established expertise in conducting these sorts of detailed physiological studies.

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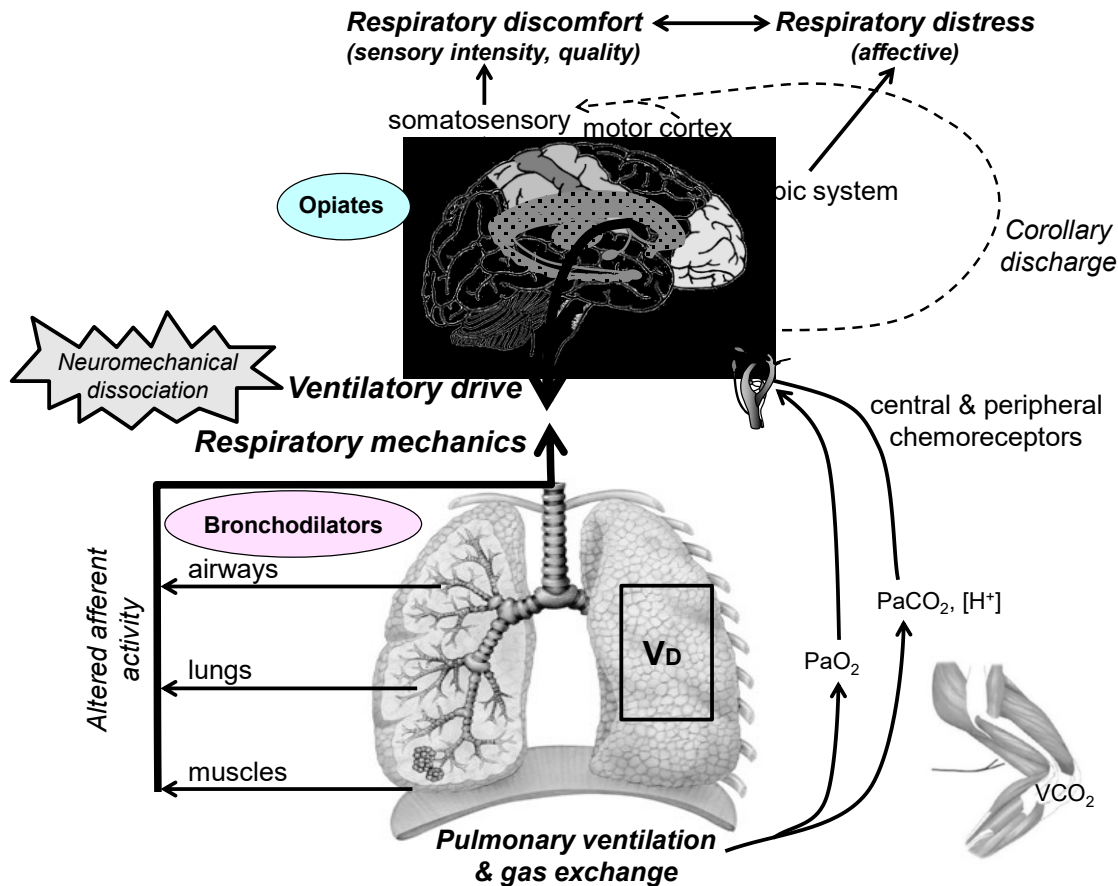
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APPENDIX 1

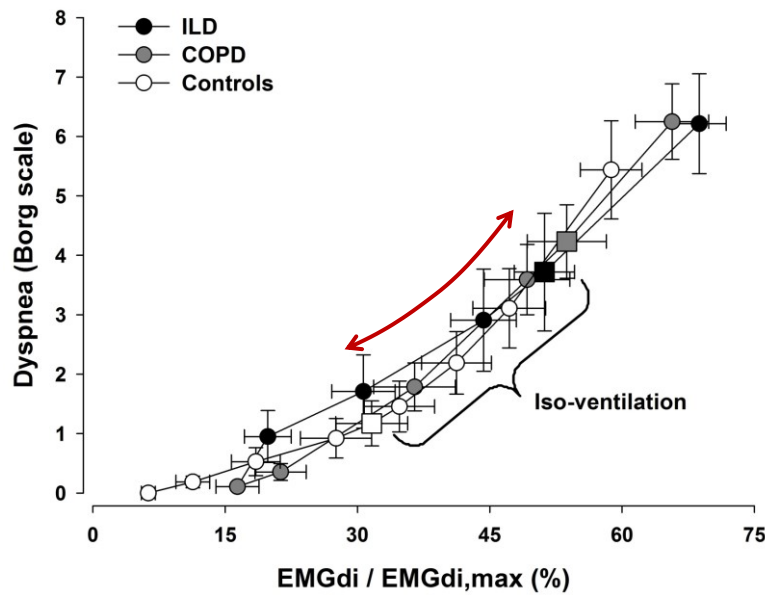
A Neurobiological Model of Dyspnea



Neural inputs that reach the somatosensory cortex and contribute to dyspnea come from: 1) altered afferent information from receptors in the airways (pulmonary stretch receptors, C-fibers), lungs (pulmonary stretch receptors, C-fibers, J-receptors) and from peripheral locomotor and respiratory muscles (muscle spindles, Golgi tendon organs, type III and IV afferents); 2) feedback from central and peripheral chemoreceptors regarding adequacy of pulmonary ventilation and gas exchange; and 3) increased central corollary discharge from brainstem and cortical motor centers. When the mechanical/muscular response of the respiratory system is constrained below the level dictated or pre-programmed by central respiratory motor drive, then the intensity of “respiratory discomfort” (i.e., the sense of *unsatisfied inspiration*) increases in proportion to the widening disparity between drive and mechanics, i.e., neuromechanical dissociation. Increased activation of limbic structures as a result of neuromechanical dissociation likely contributes to “respiratory distress.” Bronchodilators and opiates have different sites of action in this model. Abbreviations: PaCO₂ = partial pressure of arterial carbon dioxide; [H⁺] = hydrogen ion concentration; PaO₂ = partial pressure of arterial oxygen; VCO₂ = carbon dioxide output. [Adapted from: Mahler DA, O'Donnell DE. *Chest* 2015;147:232-241, and O'Donnell DE, et al. *Respir Physiol Neurobiol* 2009;167:116-32.]

APPENDIX 2

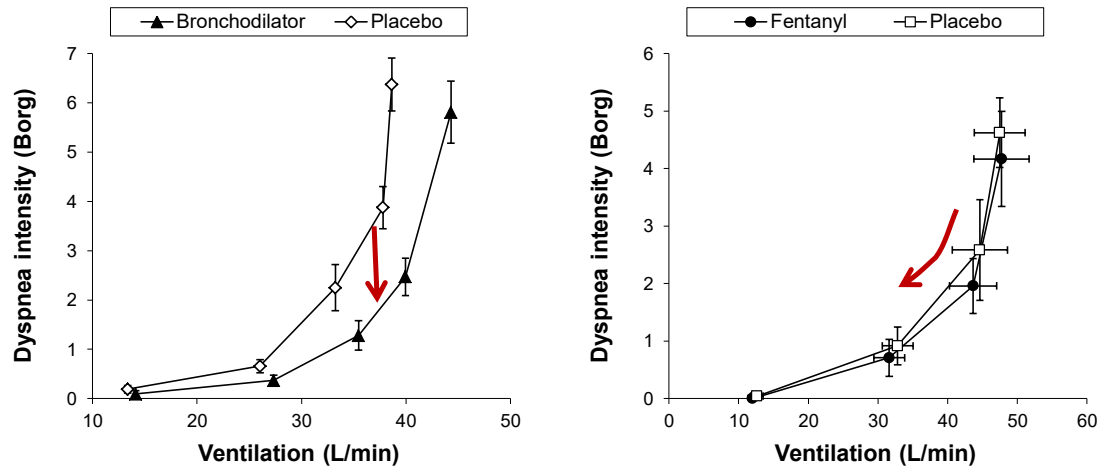
Relationship between Exertional Dyspnea Intensity and Inspiratory Neural Drive



The relationship between exertional dyspnea intensity and an index of inspiratory neural drive to the diaphragm ($EMG_{di}/EMG_{di,max}$) is shown during incremental cycle exercise in patients with interstitial lung disease (ILD), patients with COPD and age-matched healthy controls ($n=16$ per group). This relationship was similar across groups. Values are mean \pm SEM. Square symbols represent tidal volume-ventilation inflection points. $EMG_{di}/EMG_{di,max}$ = inspiratory diaphragm electromyography as a fraction of maximum. [Adapted from: Faisal A, et al. *Am J Respir Crit Care Med* published online September 25, 2015 as doi: 10.1164/rccm.201504-0841OC]

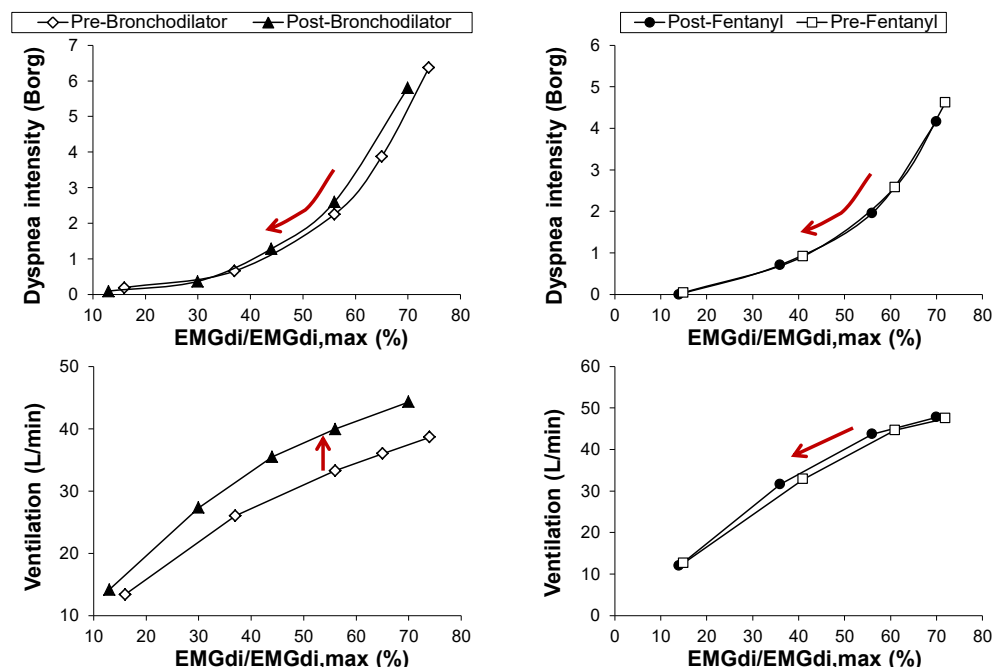
APPENDIX 3

Exertional Dyspnea Intensity in Response to Bronchodilators and Opiates



Dyspnea-ventilation relationships during constant-work rate exercise in COPD are shown from two different randomized, placebo-controlled crossover studies performed at the Respiratory Investigation Unit. **Bronchodilators (left):** In response to nebulized bronchodilator (ipratropium 0.5mg + salbutamol 2.5mg), dyspnea fell significantly for a given ventilation in 16 patients with moderate-to-severe COPD [Peters M, et al. Thorax 2006;61:559-567]. Reductions in dyspnea intensity were attributed to improvements in respiratory mechanics (i.e., an increased inspiratory capacity allowed greater tidal volume expansion). **Opiates (right):** In response to nebulized fentanyl 50µg (right), dyspnea-ventilation relationships were unaltered in 12 patients with COPD [Jensen D, et al. J Pain Symptom Manage 2012;43:706-719]. Decreases in ventilation with inhaled fentanyl resulted from decreases in breathing frequency (prolongation of expiratory time), with little change in respiratory mechanical measurements.

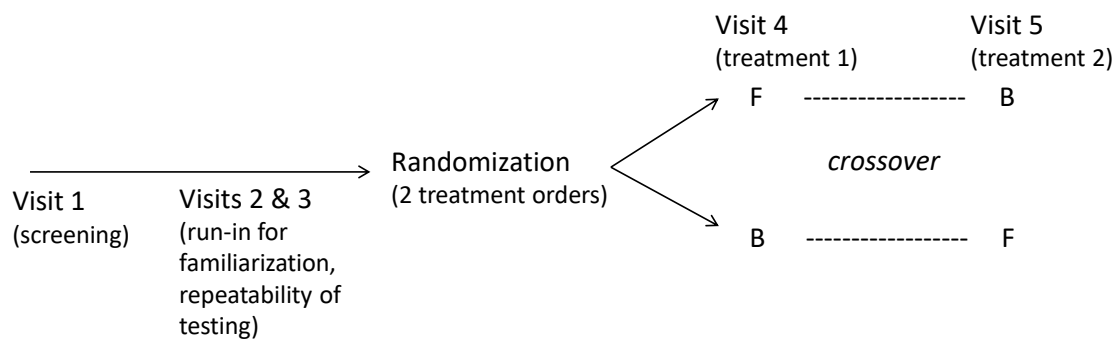
Hypotheses: The relationship between dyspnea intensity and inspiratory neural drive to the diaphragm (EMGdi/EMGdi,max) will remain constant across both interventions (compared with placebo or pre-treatment conditions). Therefore: 1) improved respiratory mechanical/muscle function after a bronchodilator will necessitate lower inspiratory neural drive for a given ventilation; and 2) a reduction in inspiratory neural drive after fentanyl will result in a proportional decrease in ventilation. A schematic illustration of these responses is shown below.



APPENDIX 4

Study Design

Two-treatment crossover study (Fentanyl, Bronchodilator)



Experimental visits

Pre-treatment:

Insertion of EMGdi-pressure catheter
PFTs (spirometry, body plethysmography)
Constant work rate exercise (4-min exercise test)
breathing 21% oxygen

Treatment:

15-min nebulization of either fentanyl or bronchodilator

30-min rest

Post-treatment:

PFTs (spirometry, body plethysmography)
Constant work rate exercise (4-min exercise test)
breathing either 30% oxygen (Fentanyl) or 21% oxygen
(bronchodilator)

Primary endpoint:
 Δ Dyspnea at 4-min
of exercise