EFFECT OF NEBULIZED FENTANYL CITRATE ON DYSPNEA DURING EXERCISE WITH AND WITHOUT EXTERNAL THORACIC RESTRICTION IN HEALTHY MAN

by

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ABSTRACT

Background & rationale. Spirometrically-defined restrictive lung impairment is common in the general population of North American adults, with a prevalence ranging from 12.5% to 14.5%. Although the severity of restricted spirometry is 'mild' in the vast majority of these individuals, it is nevertheless associated with more activity-related dyspnea and worse health status than adults with 'normal' spirometry. Indeed, exertional dyspnea is a hallmark symptom of patients with chronic restrictive pulmonary disorders, including interstitial lung disease, diseases of the chest wall and neuromuscular disorders. It follows that alleviating dyspnea is among the principal goals in the clinical management of individuals with restrictive lung disorders. Nevertheless, few therapeutic options exist for the effective management of exertional dyspnea in persons with restrictive pulmonary disorders, which makes research into this area both timely and clinically relevant.

Based on the results of numerous *in vitro* studies, there are reasons to believe that inhalation of nebulized opioids selective for the mu (μ)-receptor subtype may be successful in relieving dyspnea during exercise by altering the activity of opioid receptors located in the tracheobronchial tree and alveoli. Limited data currently exist on the efficacy of nebulized opioids for the relief of dyspnea on exertion in restrictive pulmonary disorders.

Research aims. In light of the information cited above, the aims of this study were, first, to test the hypothesis that single-dose inhalation of a μ-opioid receptor agonist relieves dyspnea during exercise in the presence of 'abnormal' restrictive ventilatory constraints and, second, to identify the physiological mechanisms underlying these improvements.

Methods. In a randomized, double-blind, placebo-controlled cross-over study, we examined the effect of high-dose nebulized fentanyl citrate (250 μg), external thoracic restriction sufficient to mimic a 'mild' restrictive lung deficit, and their interaction on detailed assessments of dyspnea, ventilation, breathing pattern, operating lung volumes, diaphragmatic EMG and respiratory muscle function during constant work rate cycle exercise testing at 85% of maximum work rate in 14 healthy men aged 24.9 ± 1.4 years.

Results. By design, external thoracic restriction by chest wall strapping decreased vital capacity by ~20% and mimicked the negative consequences of a 'mild' restrictive lung disorder on exercise tolerance and on dyspnea, breathing pattern, operating lung volumes, diaphragmatic EMG and respiratory muscle function during exercise. In contrast to our *a priori* hypothesis, however, nebulized fentanyl neither relieved dyspnea during exercise nor influenced the integrated physiological response to exercise with and without chest wall strapping.

Conclusions & implications. The results of this study do not support a role of intrapulmonary opioids in the neuromodulation of exercise dyspnea (at least not in healthy young men) nor do they provide a physiological rationale for the use of nebulized opioids in the pharmacological management of dyspnea due to restrictive lung disorders, particularly those arising from diseases of the chest wall (e.g., kyphoscoliosis, pectus excavatum) and without chronic airway inflammation.

RÉSUMÉ

Contexte & justification. La déficience restrictive pulmonaire, qui est définie par la spirométrie, est commune dans la population générale d'adultes nord-américains, avec une prévalence allant de 12,5 % à 14,5 %. Bien que la gravité de la spirométrie restrictif soit "douce" dans la grande majorité de ces personnes, elle est néanmoins associée au plus de dyspnée lors d'activités physiques et à l'état de santé pire que d'adultes avec la spirométrie normale. En effet, la dyspnée lors d'activités physiques est un symptôme caractéristique de patients souffrant de maladies chroniques restrictives pulmonaires, notamment les maladies pulmonaires interstitielles, les maladies de la paroi thoracique et les maladies neuromusculaires. Il s'ensuit que le soulagement de la dyspnée est parmi les objectifs principaux de la gestion clinique des individus souffrants de maladies restrictives pulmonaires. Néanmoins, quelques options thérapeutiques existent pour la gestion efficace de la dyspnée lors d'activités physiques de personnes souffrantes de troubles restrictives pulmonaires, ce qui rend la recherche dans ce domaine tant opportune et pertinente sur le plan clinique.

Basé sur les résultats de nombreuses études in vitro, il y a des raisons de croire que l'inhalation d'opioïdes par nébulisation sélective des récepteurs de type-μ peut être efficace à soulager la dyspnée pendant l'exercice en modifiant l'activité des récepteurs opioïdes situé dans l'arborescence tracheobronchial et alvéoles. Peu de données existent actuellement sur l'efficacité des opioïdes par nébulisation pour le soulagement de la dyspnée à l'effort restrictif de maladies pulmonaires.

Objectifs de la recherche. Basé sur l'information citée ci-dessus, les objectifs de cette étude étaient, premièrement, de tester l'hypothèse selon laquelle l'inhalation d'une dose unique d'une agoniste des récepteurs opioïde de type-μ permet le soulagement de la dyspnée pendant l'exercice en présence de restriction ventilatoire 'anormal' externe et, deuxièmement, d'identifier les mécanismes physiologiques sous-jacents à ces améliorations.

Méthodes. Dans une étude randomisée, en double aveugle, croisée et contrôlée versus placebo, nous avons examiné l'effet d'une dose élevée de fentanyl citrate (250 μg) par nébulisation, la restriction thoracique externe suffisante pour imiter un déficit restrictive pulmonaire "doux", et leur interaction sur l'évaluations détaillées de la dyspnée, de la ventilation, du rythme respiratoire, des volumes d'exploitation pulmonaires, de l'EMG diaphragmatique et la fonction des muscles respiratoires pendant l'exercise de travail constant sur vélo à 85% de rythme maximum de 14 hommes en bonne santé âgés de 24,9 ± 1,4 ans.

Résultats. Par conception, la restriction thoracique externe par un cerclage thoracique a diminué la capacité vitale par ~ 20% et imité des conséquences négatives d'un déficit restrictive pulmonaire "doux" â l'endurance physique, la dyspnée, la respiration, les volumes d'exploitation pulmonaires, l'EMG diaphragmatique et la fonction des muscles respiratoires pendant l'exercice. Contrairement à nos hypothèse a priori, cependant, la nébulisation de fentanyl ni a soulagé la dyspnée pendant l'exercice ni a influencé la réponse physiologique intégrée de l'exercise avec et sans cerclage thoracique.

Conclusions & implications. Les résultats de cette étude ne prennent pas en charge un rôle d'opioïdes intra-pulmonaire dans la neuromodulation de dyspnée lors d'activités physiques (du moins pas en hommes jeunes et en bonne santé) et ne fournissent pas une raison physiologique de l'utilisation d'opioïdes par nébulisation dans la gestion pharmacologique de la dyspnée à cause de troubles restrictives pulmonaires, en particulier ceux découlant de maladies de la paroi thoracique (p. ex., kyphoscoliosis, le pectus excavatum) et sans maladies chroniques inflammatoires des voies respiratoires.

PREFACE & CONTRIBUTION OF AUTHORS

H.G. Kotrach was the principal contributor to the collection, analysis, and interpretation of data; and was primarily responsible for thesis/manuscript preparation.

Dr. Bourbeau served as medical supervisor, and contributed to the review of the protocol, interpretation of data and review of the thesis/manuscript.

As principal investigator, ***Dr. Jensen*** designed and secured financial support of the experiments, and contributed to all aspects of the study. He is the guarantor of the thesis/manuscript and takes responsibility for the integrity of the data and accuracy of the data analysis.

CHAPTER ONE: REVIEW OF THE LITERATURE

1.1. Dyspnea & its significance.

Dyspnea has been defined by the American Thoracic Society as the "subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity" [1]. In the general population, activity-related dyspnea has a prevalence of 13-30% [2] and has emerged as an independent predictor of morbidity and all-cause mortality [3-6]. For example, in the United States, the symptom of dyspnea is reportedly responsible for 3-4 million emergency care visits annually [7] and is second to chest pain as the most common reason for seeking emergency medical care [8].

In the general population of adults in Canada [9], the United States [10] and Spain [11], the prevalence of spirometrically-defined restrictive lung impairment is 12.7-14.2%. Although the severity of restricted spirometry is 'mild' in over 95% of these individuals, it is nevertheless associated with more activity-related dyspnea and worse health status than adults with 'normal' spirometry [11, 12].

Clinically, dyspnea on exertion is recognized as the cardinal symptom of patients with restrictive lung disorders [13], such as interstitial lung disease (ILD), diseases of chest wall (e.g., kyphoscoliosis) and neuromuscular disease [13-18]. For example, Bjoraker et al.[19] and Watters et al.[20] found that 90-93% of patients with ILD self-reported dyspnea at initial evaluation/diagnosis. In these patients, the symptom of dyspnea contributes importantly to physical activity limitation and is associated with adverse health status/outcomes, including quality of life, anxiety/depression, diabetes, cardiovascular disease, hypertension and all-cause mortality [11, 21-25]. Alleviating dyspnea is therefore among the principal goals in the clinical management of individuals with restrictive lung disorders [13, 16, 26].

1.2. Mechanisms of dyspnea during exercise in restrictive lung disorders.

Although the pathophysiological underpinnings of ILD, diseases of the chest wall and neuromuscular disease are markedly different, their impact on static and dynamic respiratory mechanical and muscular function at rest and during exercise is broadly similar. In persons with restrictive pulmonary disorders, the respiratory system's sigmoid pressure-volume curve is contracted along its volume axis, reflecting reduced total respiratory system compliance [14, 27-29] (**Fig. 1.1**).

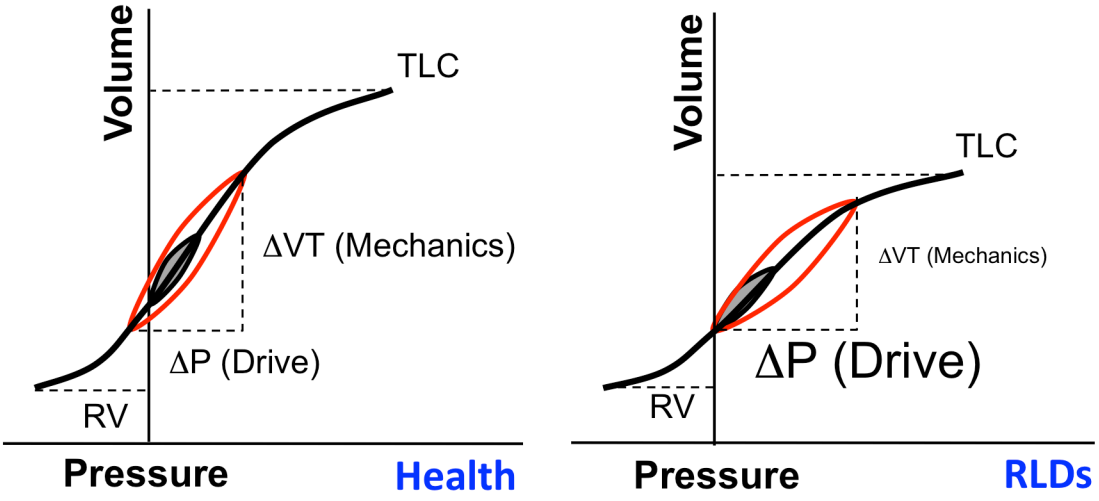

Fig. 1.1. Pressure-volume (P-V) relationships of the respiratory system in health and restrictive lung disorders (RLDs). ΔP: change in respiratory muscle pressures (represents neural respiratory drive); ΔVT: change tidal volume (represents the mechanical response of the respiratory system); RV: residual volume; TLC: total lung capacity. Modified from O'Donnell et al.[30]

Reductions in total respiratory system compliance are caused by: (1) increased inward recoil pressure of the lungs at any given lung volume (i.e., reduced lung compliance) due to the accumulation of fibrotic tissue in the pulmonary parenchyma [16, 29]; and/or (2) reduced chest wall compliance due to deformities in the skeletal structure of the chest wall, the spine and its articulations in diseases like kyphoscoliosis and ankylosing spondilitis. In these individuals, the

reduced respiratory system compliance imposes a greater load on the already weakened respiratory musculature [15, 29, 31-34] and is associated with reductions in static lung volumes/capacities, including total lung capacity, inspiratory capacity, inspiratory reserve volume, tidal volume (V_T), forced vital capacity and forced expiratory in 1-sec (**Figs. 1.2 & 1.3**) [35-39].

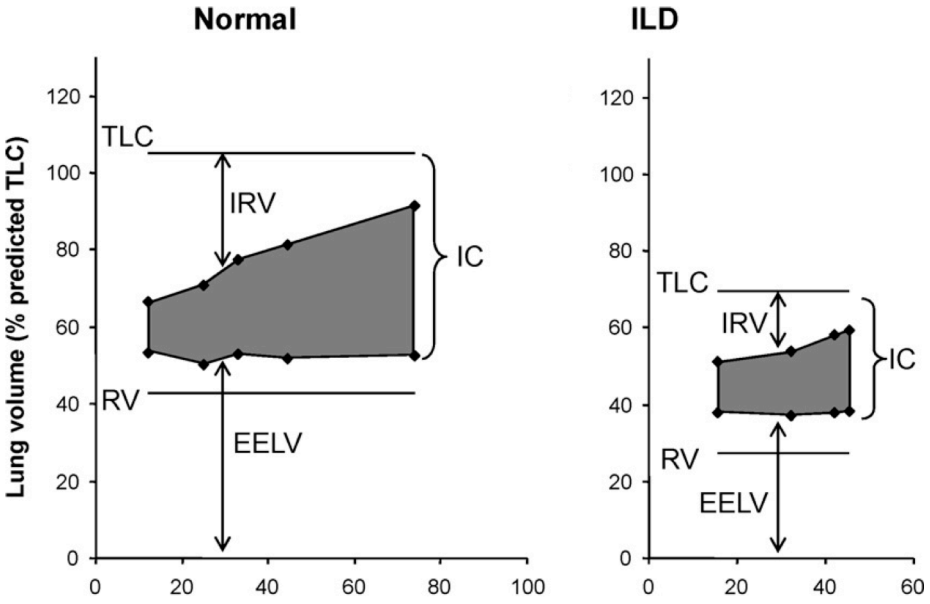

Fig. 1.2. Behavior of dynamic operating lung volumes as ventilation increases during exercise in health and in patients with moderate-to-severe interstitial lung disease (ILD). TLC: total lung capacity; IRV: inspiratory reserve volume; IC: inspiratory capacity; RV: residual volume; EELV: end-expiratory lung volume. Modified from O'Donnell et al.[23]

It follows that during exercise in restrictive lung disorders, V_T is forced to expand on the upper alinear (non-compliant) portion of the respiratory systems sigmoid pressure-volume curve where there is increased elastic loading and functional weakening of the inspiratory pump muscles, namely the diaphragm (**Fig. 1.1**). Under these circumstances, breathing pattern is more tachypneic than normal (**Fig. 1.4**) [14, 40], while abnormally high levels of neural respiratory (inspiratory) drive and contractile respiratory muscle effort (pressure) requirements are needed to support the increased

ventilatory demands at rest and during the physiological stress of exercise (**Fig. 1.4**) [14, 41] and hypercapnia-induced hyperpnea [42].

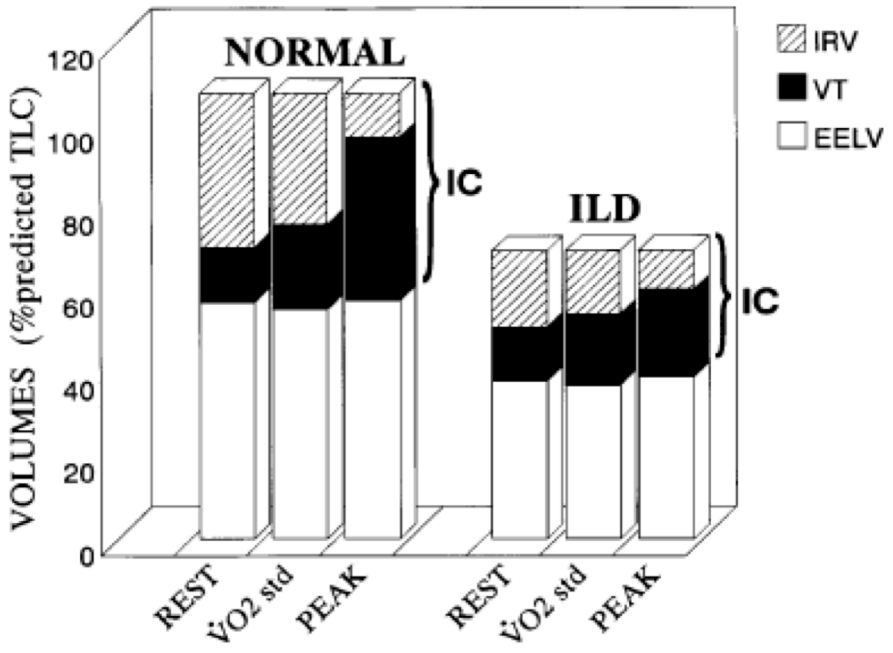

Fig. 1.3. Comparison of operational lung volumes (expressed as a percentage of the predicted total lung capacity (TLC)) between normal subjects and patients with interstitial lung disease (ILD) at rest, during exercise at 50% of maximal oxygen consumption (VO2 std), and at peak exercise. IRV, inspiratory reserve volume; VT, tidal volume; EELV, end-expiratory lung volume; IC, inspiratory capacity. Adapated from O'Donnell et al.[14]

Based on a comprehensive review of the literature, O'Donnell and colleagues [23] hypothesized that the combination of abnormalities in neural respiratory drive and dynamic respiratory mechanical and muscular function (i.e., neuromechanical uncoupling of the respiratory system) may form the mechanistic basis of dyspnea during exercise in restrictive pulmonary disorders. According to this hypothesis, the increased perception of activity-related dyspnea in restrictive pulmonary disorders reflects the widening disparity (as exercise progresses) between the magnitude of increased central respiratory motor output command (as sensed by increased 'central

corollary discharge' to sensory areas of the brain) and the simultaneous mechanical and muscular response of the respiratory system, particularly as it relates to impaired V_T expansion [23].

The idea that neuromechanical uncoupling is likely responsible for increased activity-related dyspnea in restrictive pulmonary disorders is supported by the results of O'Donnell et al.[14] who found that: (1) dyspnea intensity ratings are higher than normal during incremental cycle ergometer exercise in patients with ILD (**Fig. 1.4**) and that they correlated well with indices of dynamic mechanical constraints on V_T expansion; and (2) the ratio of contractile respiratory muscle effort (tidal esophageal pressure swing expressed as a percentage of maximum inspiratory pressure) to thoracic volume displacement (V_T expressed as a percentage of predicted vital capacity) – a crude index of neuromechanical uncoupling – is significantly higher than normal during exercise in patients with ILD (**Fig. 1.4**).

Alternatively, a recent report from our laboratory by Mendonca et al.[43] has provided preliminary evidence to suggest that the increased perception of dyspnea during exercise in restrictive pulmonary disorders may not reflect neuromechanical uncoupling of the respiratory system *per se*, but rather the awareness of increased neural respiratory drive needed overcome the 'abnormal' restrictive constraints on V_T expansion and maintain an appropriate ventilatory response to exercise.

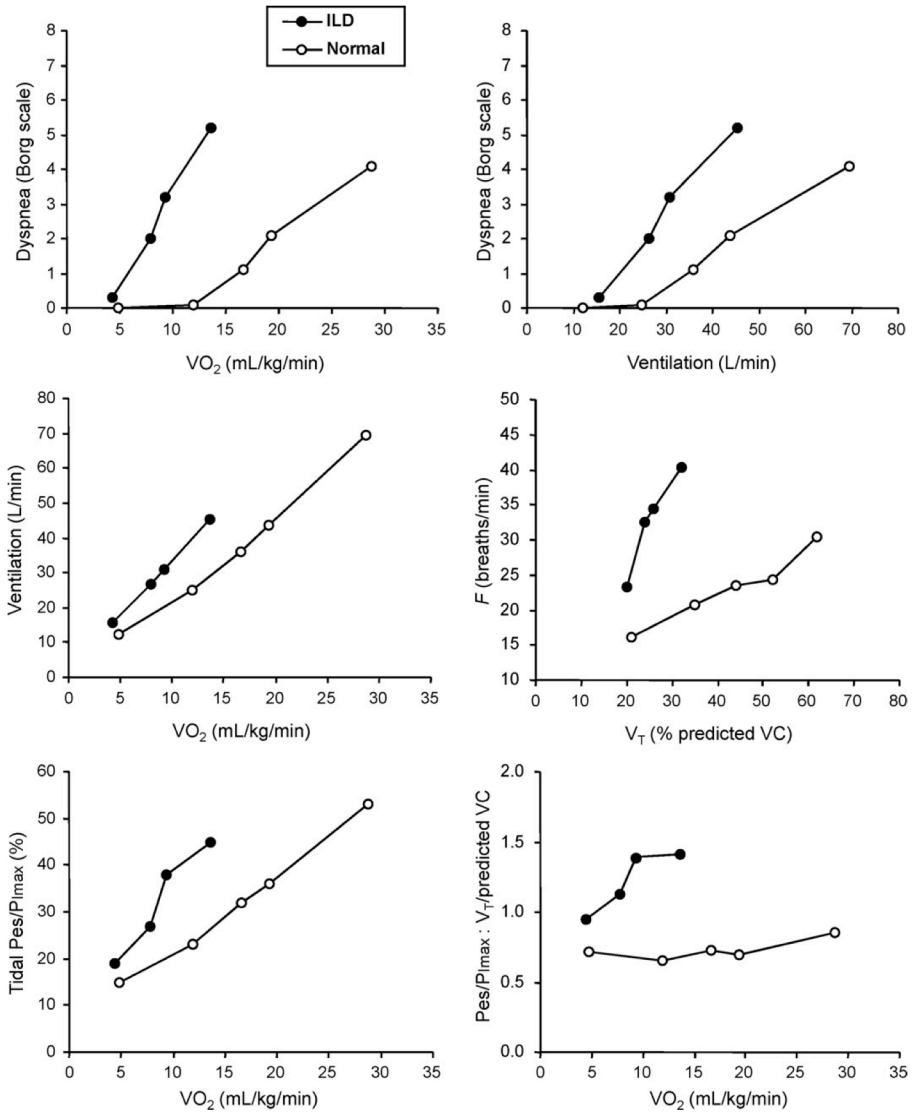

Fig. 1.4. Perceptual and ventilatory responses to symptom-limited incremental cycle exercise in patients with interstitial lung disease (ILD) and age-matched healthy control subjects. In patients with ILD compared with health: Borg 0-10 scale intensity ratings of dyspnea are greater for a given rate of O_2 consumption (VO_2) and ventilation during exercise; ventilation is greater for a given VO_2 during exercise; breathing pattern is more rapid and shallow; contractile respiratory muscle effort (defined as the tidal swing in esophageal pressure relatively to maximum inspiratory pressure; Tidal Pes/PImax) is greater; the ratio of contractile respiratory muscle effort (Tidal Pes/PImax) to thoracic volume displacement (tidal volume expressed as a percentage of predicted vital capacity; V_T/predicted VC) – a crude index of neuromechanical uncoupling of the respiratory system – is greater; *F*, breathing frequency. Adapted from O'Donnell et al.[14, 23]

1.3. Conventional dyspnea management strategies in restrictive pulmonary disorders.

Although our understanding of the mechanisms of increased activity-related dyspnea in restrictive pulmonary disorders continues to evolve, effective management of this symptom in these patients remains a challenge for healthcare providers. As illustrated in **Fig. 1.5**, the clinical management of restrictive pulmonary disorders, namely ILD, is focused on treating the underlying disease (with anti-fibrotic agents, for example) and managing co-morbidities such as cardiovascular deconditioning and hypoxemia through pulmonary rehabilitation and domiciliary oxygen, respectively [16, 17, 44-46].

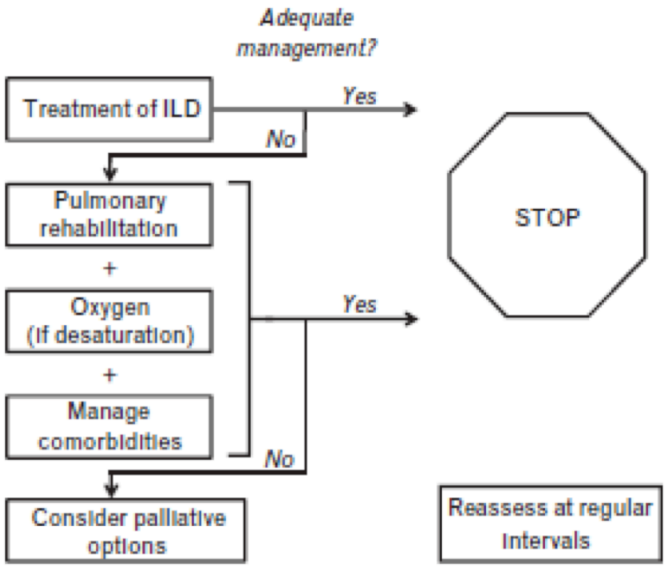

Fig. 1.5. Management of dyspnea in patients with interstitial lung disease (ILD). If the underlying pathology is untreatable, a combination of pulmonary rehabilitation, oxygen therapy and managing comorbidities should be attempted. Otherwise, palliative options (e.g., opioids) should be considered. Adapted from Collard & Pantilat [17].

Although these disease-specific interventions often translate into meaningful improvements in dyspnea and health status [16, 17, 47, 48], many patients remain troubled by dyspnea and limited in their ability to perform activities of daily living. Under these circumstances, evidence-based

clinical practice guidelines recommend that opioid analgesic drugs may be used to help manage refractory symptoms [13, 26]. Indeed, it is now relatively well established [49] that opioid medications administered systemically (e.g., oral, intravenous, sublingual, transdermal) are both safe and effective at relieving refractory dyspnea in patients with advanced cardiopulmonary disease, including restrictive pulmonary disorders [50, 51]. For example Allen et al. reported that low-dose (2.5 mg) diamorphine administered subcutaneously relieved dyspnea without any untoward side-effects in 11 elderly and opioid-naïve patients with end-stage idiopathic pulmonary fibrosis [52]. Despite the experimental and clinical evidence supporting their effectiveness and safety, many healthcare providers remain skeptical on the use of systemic opioids for the management of dyspnea in patients with chronic pulmonary disorders for fear of respiratory depression and other potential adverse side effects such as nausea, constipation, apathy, sedation, *etc.* [1, 53-55].

1.4. Inhaled opioids: an alternative dyspnea-relieving approach?

In theory, inhalation of nebulized opioids may circumvent these adverse systemic side effects, while still helping to relieve dyspnea and improve exercise tolerance. Three classes of opioid receptors – mu (μ), kappa and delta – have been identified in the alveolar walls and in the trachea and main bronchi [56] of animal and human lungs, thus making the respiratory system a promising (theoretical) target for inhaled opioids in the pharmacological management of dyspnea [56-59]. From the patient perspective, Simon et al.[60] recently reported that inhalation was identified as the most accepted and preferred route of opioid administration (compared to oral,

sublingual, intranasal, buccal and transmucosal) by 119 patients suffering from refractory dyspnea due to advanced disease.

1.5.The signal transduction mechanism of opioid receptors.

To comprehensively understand the function and potential benefit of inhaled opioids in the management of dyspnea, it is important to briefly review the acute and chronic intracellular signal transduction mechanism(s) of opioid receptors (**Fig. 1.6**). Acutely, after binding of either an endogenous (e.g., β-endorphin) or exogenous (e.g., morphine) opioid ligand to its 7-transmembrane G-protein coupled receptor (GPCR), there is a receptor conformational change that results in intracellular coupling of G-proteins to the opioid receptor. Consequently, guanosine diphosphate (GDP) is substituted with guanosine triphosphate (GTP) and the G-protein complex dissociates into Gα and Gβ-γ subunits. This inhibits Ca^{2+} influx by closing the voltage-gated calcium channel (VGCC); stimulates K^{+} outflux; and inhibits the action of adenylyl cyclase, thus decreasing intracellular levels of cyclic AMP (cAMP). Collectively, these intracellular changes decrease the excitability and the transmission of neural impulses across the nerve by reducing neurotransmitter release [61]. Furthermore, decreasing the level of cAMP causes a reduction in the level of cAMP-dependent protein kinase A (PKA), which alters μ-opioid receptor gene transcription through series of molecular changes downstream towards the nucleus [62, 63].

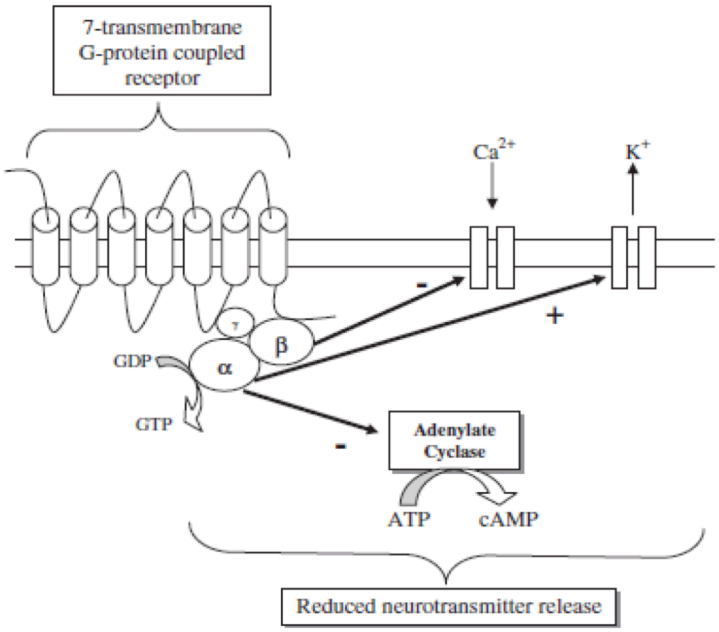

Fig. 1.6. The signal transduction mechanism of opioid receptor activation**.** Binding of the opioid ligand to the 7-transmembrane G-protein coupled opioid receptor initiates a cellular mechanism through the G-protein, which stimulates K^+ efflux, inhibits both Ca^{+2} efflux and Adenylate Cyclase activity. Adapted from McDonald & Lambert [64].

Chronically, the activation of opioid receptors causes an uncoupling between the opioid receptor and the adenylyl cyclase system leading to receptor desensitization and subsequent inhibition of cAMP production [61]. Opioid receptor desensitization happens by three mechanisms: (1) receptor phosphorylation; (2) receptor internalization and/or sequestration; and/or (3) receptor down-regulation. Many enzymes such as phosphokinase-C and GPCR-kinases can lead to receptor desensitization through receptor phosphorylation. This brings Arrestin molecules to the receptor, which forms Arrestin-receptor complexes that sterically prevents G-protein coupling and promotes receptor internalization and possibly thereafter ending in receptor lysosomal degradation. This is one of the mechanisms underlying opioid tolerance, dependence and withdrawal [62].

1.6.Potential (peripheral) mechanisms of dyspnea relief with inhaled opioids.

As alluded to previously, researchers have identified a network of opioid receptors located in sensory afferent nerves (e.g., C-fibers) within the tracheobronchial tree and the alveoli of the mammalian (both human and non-human) respiratory system [56, 58, 59, 65-68]. It follows that intrapulmonary opioid receptors may be easily accessible to inhaled treatment and have thus been the focus of much attention and optimism as a pharmacological target for the relief of dyspnea.

The central mechanisms whereby systemic opioids relieve dyspnea are relatively well established and include (but are not necessarily limited to) central desensitization to dyspneogenic stimuli [69-73] and reduced central respiratory drive and corollary discharge [72-76]. By contrast, our understanding of the peripheral mechanism(s) of action of opioid analgesics continues to evolve and, until now, have been provided primarily by *in vitro* studies with isolated bronchi from non-human mammals such as pigs and guinea pigs. What follows is a summary of the potential mechanisms whereby inhaled opioids of the μ-receptor subtype may directly and/or indirectly contribute to the relief of dyspnea in humans *in vivo*:

1) Direct effect of inhaled opioids on cholinergic neurotransmission and contraction of the airway smooth muscle (Fig. 1.7) [58]. Numerous *in vitro* studies using isolated bronchi have shown that electrical field stimulation (EFS) of the parasympathetic neural innervation of the airway smooth muscle (ASM) causes the release of the neurotransmitter, acetylcholine (Ach), from post-ganglionic nerves [77-81]. Additionally, the topical application of agonist drugs selective for

the μ-opioid receptor subtype in isolated human [78, 82] and animal airways [77, 82-89] almost completely inhibits EFS-induced ASM contraction by inhibiting pre-junctional release of Ach from cholinergic (vagal) efferent nerves. Importantly, this inhibition is completely prevented in the presence of naloxone, a μ-opioid receptor antagonist [77], confirming a mechanistic role of μ-opioid receptors in cholinergic neurotransmission and bronchoconstriction of the ASM. Based on these findings, it is reasonable to postulate that inhaled opioids may contribute to the relief of dyspnea by altering the activity of intra-pulmonary μ-opioid receptors and reflexively reducing cholinergic ASM tone (i.e., bronchodilatation), with attendant improvements in dynamic respiratory mechanical and muscular function during exercise.

2) Inhibition of neurogenic airway inflammation with concomitant improvements in static and dynamic airway function *via* binding of inhaled opioids to μ-opioid receptors on bronchopulmonary C-fibers. Neurogenic airway inflammation is associated with an up-regulation of three neural processes: (1) The synthesis of μ-opioid receptors in neurocyte cell body in the dorsal root ganglia (DRG) of the spinal cord [61, 90, 91]; (2) The unidirectional axonal transport of the μ-opioid receptors between the neurocyte cell body and its peripheral sensory nerve ending in the airways (e.g., bronchopulmonary C-fibers) [90, 92]; and (3) The increased permeability of the perineural sheath that surrounds the C-fibers [91, 93]. The upregulation of these three processes increase the density and accessibility of μ-opioid receptors on sensory nerve endings [61]. In theory, these neural adaptations may allow μ-opioid receptor agonists to reduce airway resistance and inflammation (with attendant relief of dyspnea) by inhibiting neurogenic mucus hypersecretion [94], plasma extravasation [94, 95], goblet cell secretion [96], and/or (iv) the

release of powerful inflammatory neuropeptides from bronchopulmonary C-fibers as shown in (**Fig. 1.7**) [56, 68, 97-99].

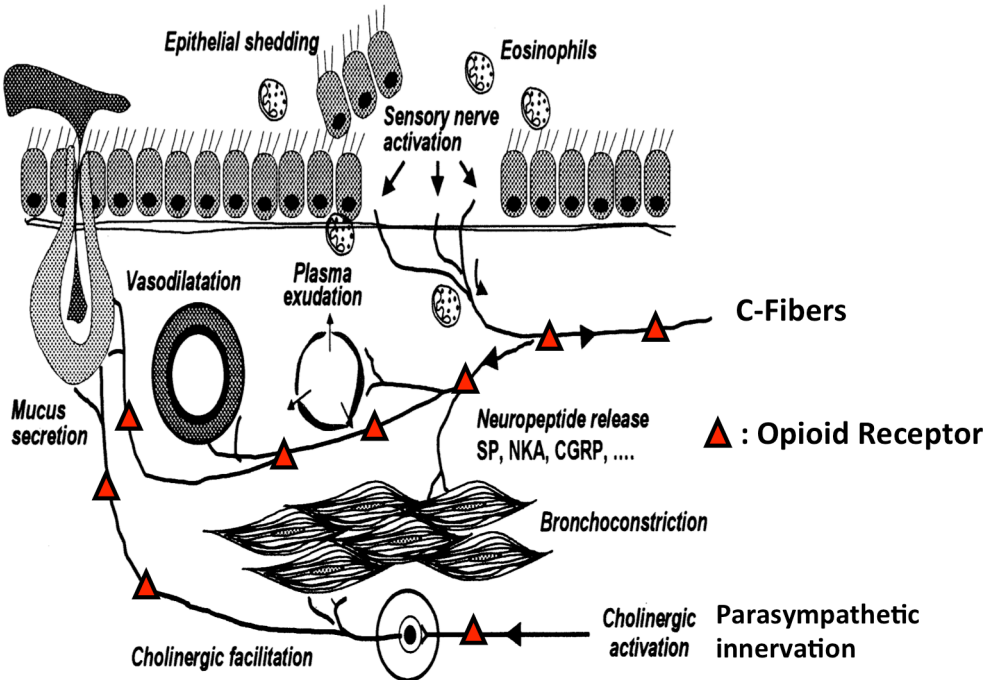

Fig. 1.7. Neurogenic inflammation in the airways under the influence of sensory C-fibers activation (refer to text for details). SP: substance P; NKA, Neurokinin A; CGRP, calcitonin gene-related peptide. Adapted from Barnes [97].

3) Direct effect of inhaled opioids on μ-opioid receptors localized on bronchopulmonary C-fibers [56, 68, 95]. As reviewed in detail elsewhere [100], bronchopulmonary C-fibers have been implicated in the etiology of dyspnea. Available evidence suggests that, in response to bronchopulmonary C-fiber stimulation, sensory (afferent) signals are sent *via* the vagus nerve to sensory areas of the brain (e.g., insula) where they are further processed and consciously perceived as dyspnea [100]. Indeed, inhalation of nebulized prostaglandin E_2 - a selective bronchopulmonary C-fiber agonist - has previously been shown to increase the intensity of dyspnea during exercise in healthy adults [101]. The corollary of these findings is that inhaled

nebulized opioids may relieve dyspnea by decreasing neural activation of bronchopulmonary C-fibers (**Fig. 1.7**).

1.7.Theory vs. practice: do nebulized opioids relieve dyspnea in humans?

Although the results of *in vitro* studies support their use (theoretically) in the management of dyspnea, much controversy exists regarding the efficacy of nebulized opioids to relieve dyspnea in symptomatic patients with cardiopulmonary disease [49, 57, 102-106]. Several anecdotal reports and non-randomized case control studies in patients with cystic fibrosis and cancer have provided evidence to suggest that nebulized opioids have the potential to relieve dyspnea [107-111]. In keeping with these findings, a randomized double-blind placebo-controlled cross-over study by Young et al. [112] was the first to show that low dose (5 mg) inhalation of nebulized morphine, a μ-opioid receptor agonist, improved high-intensity constant work rate cycle exercise endurance time by an average of 65-sec or 35% (*versus* +9-sec or 1% with placebo; $p<0.01$) in 11 patients with advanced lung disease: 9 with chronic obstructive pulmonary disease (COPD); 2 with ILD. Unfortunately, Young et al. did not examine the simultaneous effects of nebulized morphine on their patients' ratings of dyspnea during exercise.

A similar study by Jensen et al. [113] recently demonstrated that low dose (50 μg) nebulized fentanyl citrate, a powerful μ-opioid receptor agonist, significantly increased high-intensity constant work rate cycle exercise endurance time by ~25% ($p=0.01$ vs. placebo) in 12 patients with mild-to-severe COPD. Although nebulized fentanyl citrate had no effect on Borg 0-10 scale intensity ratings of dyspnea at a standardized submaximal time during exercise (primary

outcome variable), it was associated with a delay in the onset of intolerable dyspnea, particularly near the limits of tolerance.

A randomized double-blind clinical trial by Shohrati et al. [114] recently evaluated the effectiveness of a 1 mg daily dose of nebulized morphine sulfate for 5 days on ratings of perceived dyspnea in a group of 40 patients who developed COPD due to extensive exposure to sulfur mustard gas during the Iraq-Iran war. In this study, intensity ratings of dyspnea significantly decreased by ~25% following 5 days of treatment with nebulized morphine (compared to no change in dyspnea after 5 days of treatment with nebulized 0.9% saline placebo).

With the exception of the aforementioned studies by Young et al. [112], Jensen et al. [113] and Shohrati et al. [114], the majority of randomized controlled studies have failed to demonstrate a benefit of either low- or high-dose (1-40 mg) nebulized morphine vs. placebo on exercise tolerance and dyspnea during exercise in healthy man [115] and in patients with COPD [116-120] (refer to systematic reviews by Jennings et al. [49] and Simon et al. [104]). For example, a randomized double-blind study of 16 patients with COPD by Jankelson et al. [119] reported no significant improvement in 6-min walk distance or exertional dyspnea intensity ratings after treatment with 20 and 40 mg of nebulized morphine vs. placebo. In keeping with the negative results of these trials, an elegant study by Mahler et al. [121] recently demonstrated that oral administration of ketoconazole, a drug that selectively increased peripheral (i.e., plasma) beta-endorphin concentrations by 20% vs. placebo, had no effect on intensity and unpleasantness ratings of laboratory-induced dyspnea in 20 patients with COPD. This important study suggested that intrapulmonary opioids do not likely contribute to the neuromodulation of dyspnea in COPD

and that the established benefits of systemic opioids on dyspnea [49] most likely reflect a central nervous system mechanism of action.

Clearly, the majority of all published studies on the effect of nebulized opioids have been carried out in patients with COPD, which is reasonable considering that the (theoretical) peripheral mechanism(s) of action are likely optimized in the setting of chronic airway inflammation and tissue damage (refer to *Section 1.7*). As previously discussed (refer to *Section 1.4*), however, few therapies exist for the relief of dyspnea in persons with restrictive pulmonary disorders and the question remains whether nebulized opioids may be effective even in the absence of chronic airway inflammation. To the best of our knowledge, only one randomized trial by Harris-Eze et al. [122] has examined the effect of low-dose nebulized morphine (2.5 and 5.0 mg) on exertional dyspnea and incremental cycle exercise tolerance in 6 patients with chronic restrictive lung disease, including pulmonary fibrosis (n=3), scleroderma (n=2) and sarcoidosis (n=1). In keeping with the results from studies in patients with COPD, nebulized morphine (vs. placebo) had no effect on exercise tolerance or intensity ratings of dyspnea during exercise.

A discrepancy clearly exists between the theoretical evidence supporting the use of nebulized opioids in the management of dyspnea (refer to *Section 1.7*) and the results of most randomized studies in human participants (refer to *Section 1.8*). The reasons for this discrepancy remain unclear and conjectural, but may include any one or combination of the following: the relatively small sample sizes ($n \leq 40$) of each published study; the heterogeneity of the patients studied in terms of symptomatology and/or disease severity; the presence of 'other' dyspneogenic stimuli (e.g., co-morbidities, deconditioning, anxiety/depression, hypoxemia/hypercapnia) that may obscure the potential benefit of nebulized opioids on dyspnea; the relatively low doses of

nebulized morphine used in most studies; and the use of incremental cycle exercise tests and/or field tests (e.g., 6-min walk distance) that are known to be less responsive than high-intensity constant work rate cycle exercise tests for evaluating the efficacy of therapeutic interventions on dyspnea and exercise tolerance [123]. Furthermore, all but one [113] randomized study has used nebulized morphine, whereas the synthetic μ-opioid receptor agonist, fentanyl, may be more appropriate for pulmonary drug delivery. In this regard, fentanyl is more potent (by ~100 times) and lipophilic than morphine, has a shorter duration of activity, and does not cause the release of histamine that could, in and of itself, contribute to dyspnea *via* bronchospasm. Indeed, Simon et al. [104] and Boyden et al. [124] recently reviewed the available literature and reported that, although adequately powered randomized controlled (efficacy) trials are lacking, sufficient evidence exists to suggest a potential benefit of nebulized fentanyl for the relief of dyspnea.

1.8. Position of the Problem

The question of whether nebulized opioids may relieve dyspnea during exercise in individuals with restrictive pulmonary disorders by acting on intrapulmonary opioid receptors remains unanswered and requires further examination. Thus, the aims of this randomized, double-blind, placebo-controlled cross-over study were two-fold: First, to test the hypothesis that nebulized fentanyl would relieve dyspnea during exercise in the setting of a 'mild' restrictive lung deficit. Second, to identify the physiological mechanisms underlying these improvements. To this end, we examined the effect of high-dose (250 μg) nebulized fentanyl citrate, external thoracic restriction by chest wall strapping to reduce vital capacity by 20%, and their interaction on detailed assessments of dyspnea, ventilation, breathing pattern, dynamic operating lung volumes,

diaphragmatic EMG and respiratory muscle function during high-intensity constant work rate cycle exercise testing in healthy men aged 18-40 years.

The experimental model of chest wall strapping in health was employed because it adequately mimics (albeit acutely) the static and dynamic respiratory mechanical abnormalities [43, 125, 126] typical of restrictive pulmonary disorders (particularly those associated with diseases of the chest wall, e.g., kyphoscoliosis, pectus excavatum, ankylosing spondilitis) [23], without the potentially confounding influences of comorbidities (e.g., deconditioning, anxiety/depression) that may themselves contribute to dyspnea and mask the potential benefits of nebulized opioids in persons with chronic restrictive lung impairment.

CHAPTER TWO: EFFECT OF NEBULIZED FENTANYL CITRATE ON DYSPNEA DURING EXERCISE WITH AND WITHOUT EXTERNAL THORACIC RESTRICTION IN HEALTHY MAN

2.1. Abstract

Few therapeutic options exist for the relief of dyspnea in restrictive lung disorders. Accumulating evidence suggests that nebulized fentanyl – a μ-opioid agonist – may relieve dyspnea during exercise by modulating the activity of intrapulmonary opioid receptors. Thus, our respective primary and secondary aims were to test the hypothesis that nebulized fentanyl citrate relieves dyspnea during exercise in the presence of 'abnormal' restrictive ventilatory constraints and to identify the physiological mechanism(s) of this improvement.

In a randomized, double-blind, placebo-controlled cross-over study, we examined the effect of nebulized fentanyl citrate (250 μg), external thoracic restriction by chest wall strapping (CWS) and their interaction on detailed physiological and perceptual responses to constant work rate cycle exercise (85% of maximum incremental work rate) in 14 healthy men aged 24.9 ± 1.4 yrs (mean ± SEM). By design, CWS decreased vital capacity by ~20% and mimicked the negative consequences of a 'mild' restrictive lung disorder on exercise endurance time (EET) and on dyspnea, breathing pattern, operating lung volumes, neural respiratory drive (diaphragmatic EMG) and respiratory muscle function during exercise. Compared with placebo under both unrestricted control and CWS conditions, nebulized fentanyl citrate was devoid of adverse systemic side-effects and had no effect on EET, the integrated physiological response to exercise and/or sensory intensity and unpleasantness ratings of exertional dyspnea.

Our results do not support a role of intrapulmonary opioids in the modulation of exertional dyspnea nor do they provide a physiological rationale for the use of nebulized fentanyl citrate in the management of dyspnea due to restrictive lung disorders, particularly those arising from disorders the chest wall and not affiliated with airway inflammation.

2.2. Introduction

The prevalence of spirometrically-defined restrictive lung impairment is 12.7-14.2% among adults aged ≥40 yrs [9-11]. Restrictive lung disorders (RLDs) are often associated with interstitial lung disease (ILD) [16] and it is well established that the clinical manifestations of RLDs, namely dyspnea and activity-limitation [14, 127-130], have an adverse impact on health status and quality-of-life [17, 25, 130-132]. Alleviating dyspnea and improving exercise tolerance are therefore among the principal goals in the management of RLDs [13, 16, 26]. With the exception of pulmonary rehabilitation [48], few therapeutic options exist for the management of exertional symptoms in RLDs.

There is reason to believe that inhalation of nebulized opioids may relieve dyspnea by altering the activity of opioid receptors located in the tracheobronchial tree and alveoli [56-58, 65, 133-135]; modulating the activity of sensory (vagal) afferents, e.g., bronchopulmonary C-fibers [68, 100, 136-139]; inhibiting cholinergic neurotransmission and contraction of airway smooth muscle [77, 82, 140]; and/or inhibiting neurogenic mucus hypersecretion[99], goblet cell secretion [141] and plasma extravasation [94, 95]. From a clinical perspective, inhaled opioids are attractive because this route of opioid administration is the most accepted/preferred among dyspneic patients [60] and may be associated with no adverse side-effects [118] that have limited the widespread use of systemic opioids for relief of dyspnea [53, 54]. Nevertheless, only one randomized controlled trial (RCT) has examined the effect of nebulized morphine (2.5 and 5.0 mg) on exertional dyspnea and incremental cycle exercise capacity in 6 patients with ILD: 3 with pulmonary fibrosis, 2 with scleroderma and 1 with sarcoidosis [122]. Compared to placebo, nebulized morphine improved neither dyspnea nor

exercise tolerance. The lack of symptom relief following nebulized morphine in this study may reflect the small sample size, heterogeneity of the patients, presence of "other" dyspneogenic stimuli (e.g., co-morbidities, deconditioning, hypoxemia), the relatively low doses of morphine used and/or employment of incremental exercise tests, which are less responsive than constant work rate (CWR) tests for evaluating the efficacy of therapeutic interventions on exercise tolerance and dyspnea [123, 142].

Therefore, the purpose of our study was, first, to test the hypothesis that single-dose inhalation of a mu *(μ)*-opioid receptor agonist relieves dyspnea and improves exercise tolerance during exercise in the presence of 'abnormal' restrictive ventilatory constraints and, second, to identify the physiological mechanism(s) underlying these improvements. To this end, we examined the effect of 250 μg nebulized fentanyl citrate, external thoracic restriction sufficient to mimic a 'mild' RLD [43] and their interaction on detailed assessments of dyspnea, ventilation, breathing pattern, operating lung volumes, diaphragmatic EMG (EMGdi) and respiratory muscle function during CWR cycle exercise testing in healthy men.

2.3. Methods

Randomized, double-blind, placebo-controlled study design. After providing informed consent, healthy men aged 20-40 yrs with normal spirometry [143] recruited by word of mouth and advertisements participated in 5 testing visits. *Visit 1* included pulmonary function tests (PFTs) and an incremental cycle exercise test to determine maximal work rate (*W*max). During *Visits 2-5*, subjects completed a modified version of the Opioid-Related Symptom Distress Scale (ORSDS) [144] and performed PFTs before inhalation of a 5 mL solution containing either 0.9%

saline placebo or 250 μg of FC (Sandoz Canada Inc., Boucherville, QC, Canada) administered by means of a jet nebulizer (NE-C30; Omron Healthcare, Inc. Blannockburn, IL, USA) with subjects taking deep and slow tidal breaths through a mouthpiece with nasal passages occluded. Exactly 30-min after nebulization, subjects completed the modified ORSDS, were fitted with the chest wall strap (if applicable) and performed PFTs followed by a CWR exercise test with added measurements of EMGdi and respiratory pressures under one of 4 conditions, randomized to order: unrestricted control + placebo; CTRL + fentanyl; external thoracic restriction by chest wall strapping (CWS) [43] to reduce slow vital capacity (SVC) by 20% of the value recorded at Visit 1 + placebo; and CWS + fentanyl. The Montreal Chest Institute's pharmacist, an unblinded third party not affiliated with recruitment or data collection/analysis, performed randomization according to a computer generated randomization list, blinding and dispensing of study medications. Visits were separated by $\geqslant$48 hrs and participants were asked to avoid alcohol, caffeine, heavy meals and exercise each test day. The study received ethical approval from the Institutional Review Board of the Faculty of Medicine at McGill University (A02-M16-13B).

Pulmonary function and exercise testing. Spirometry and SVC maneuvers were performed using automated equipment (Vmax Encore^{TM}, CareFusion, Yorba Linda, CA, USA) [145]. Exercise tests were performed on an electronically braked cycle ergometer (Ergoline 800s) using a Vmax Encore^{TM} cardiopulmonary exercise testing system (CareFusion). Incremental exercise tests were performed using established methods[43, 146]: *W*max was the highest work rate the subject was able to sustain for $\geqslant$30-sec. Constant work rate tests consisted of a steady-state resting period of $\geqslant$6-min, a 1-min warm-up at 25% *W*max followed by a step increase in work

rate to 85% *W*max.

Standard cardiopulmonary parameters were collected breath-by-breath [43, 146], while oxyhemoglobin saturation and heart rate were monitored by pulse oximeter and 12-lead electrocardiogram, respectively. Inspiratory capacity (IC) maneuvers were performed at rest, within the last 30-sec of every 2nd min during exercise and at end-exercise [43, 146]. Breath-by-breath measures of the root mean square of the crural diaphragm EMG (EMGdi,rms) and of esophageal (Pes), gastric (Pga) and transdiaphragmatic (Pdi = Pga – Pes) pressure were recorded from a combined esophageal electrode-balloon catheter (Guangzhou Yinghui Medical Equipment Ltd., Guangzhou, China) and analyzed using published methods [43, 146]. As described in detail elsewhere [43], subjects provided ratings to the following questions at rest, within the last 30-sec of every 2nd min during exercise and at end-exercise using Borg's 0-10 category ratio scale [147]: How *intense* is your sensation of breathing overall (hereafter referred to as dyspnea)? How *unpleasant* or *distressed* does your breathing make you feel? How *intense* is your sensation of *leg discomfort*? Finally, subjects verbalized their main reason(s) for stopping exercise; quantified the percentage contribution of dyspnea and leg discomfort to exercise cessation; and identified qualitative phrases that described their dyspnea at end-exercise [125].

Analysis of exercise end-points. All physiological parameters were averaged over the first 30-sec of every 2nd min during exercise and linked with symptom ratings and IC measurements collected during the last 30-sec of the same minute. Measured parameters were evaluated at 3 main time points: *Rest* was the average of the last 30-sec of the steady-state period after $\geqslant$2-

min of breathing on the mouthpiece before exercise; *Isotime* was the average of the first 30-sec of the 2nd min of the highest equivalent 2-min stage of CWR exercise completed by a given subject; and *Peak exercise* was the average of the last 30-sec of loaded pedaling, while exercise endurance time (EET) was the duration of loaded pedaling.

Data analysis. We estimated that 28 participants would provide >80% power to detect a ±1 Borg unit difference [148] in our primary outcome variable (dyspnea intensity at isotime) among the 4 conditions, assuming a two-tailed test of significance, a within-subject standard deviation of ±1 Borg 0-10 scale units and α=0.05.

The effect of nebulized fentanyl, CWS and their interaction on measured parameters at each measurement time was examined using a two-way repeated measures ANOVA with correction for multiple comparisons using Tukey's HSD test. Reasons for stopping exercise, qualitative descriptors of dyspnea at end-exercise, and ORSDS responses were assessed using frequency statistics. Significance was set at $p<0.05$.

2.4. Results

Subjects, side-effects and pulmonary function. Fourteen of 22 men who signed the consent form completed the study (**Fig. 2.1**) and their descriptive characteristics are presented in **Table 2.1**. After collapsing across conditions, no meaningful differences were observed in the percentage of subjects responding 'yes' to any one or combination of the modified ORSDS questions before vs. after nebulized placebo (25.0% vs. 28.6%) or fentanyl (28.6% vs. 42.9%). By design, CWS decreased both SVC and forced vital capacity (FVC) by ~20% (**Table 2.2**). These changes were accompanied by reductions in FEV_1 and mid-maximal expiratory flow rates, and

no change in the FEV_1/FVC ratio. Compared to placebo, nebulized fentanyl had no effect on spirometric parameters under CTRL and/or CWS conditions.

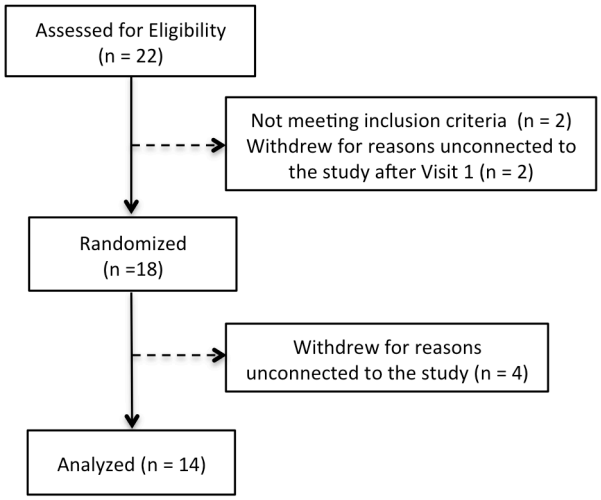

Fig. 2.1. Flow diagram: enrolment, randomization and analysis of study participants.

Table 2.1. Participant characteristics (n=14)

Parameter	
Age, yrs	24.9 ± 1.4
BMI, kg/m^2	22.8 ± 0.8
$V'O_{2,peak}$, mL/kg/min (% predicted*)	54.3 ± 2.8 (123 ± 6)
*W*max, watts (% predicted*)	241 ± 12 (104 ± 4)
SVC, L	5.24 ± 0.19
FVC, L (% predicted)	5.01 ± 0.16 (94 ± 3)
FEV_1, L (% predicted)	4.16 ± 0.15 (94 ± 3)
FEV_1/FVC, %	83.0 ± 1.7
PEFR, L/sec (% predicted)	9.74 ± 0.50 (98 ± 5)
$FEF_{25-75\%}$, L/sec (% predicted)	4.60 ± 0.25 (99 ± 5)

Values are means ± SEM. BMI, body mass index; $VO_{2,peak}$, rate of oxygen consumption at the symptom-limited peak of incremental cycle exercise; *W*max, maximum incremental cycle work rate; SVC, slow vital capacity; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1-sec; PEFR, peak expiratory flow rate; $FEF_{25-75\%}$, forced expiratory flow between 25% and 75% of the FVC maneuver. *predicted normal values derived from the ATS/ACCP Statement on Cardiopulmonary Exercise Testing[74].

Physiological responses. CWS had no influence on the ventilatory response to exercise (**Fig. 2.2**), except at peak (**Table 2.3**). By design, CWS decreased EET by 14-22% (**Table 2.3**) and mimicked the consequences of a 'mild' RLD on breathing pattern, operating lung volume and neural respiratory drive responses to exercise. For example, breathing frequency was higher, while tidal volume (V_T) and IC were lower during submaximal exercise with vs. without CWS (**Table 2.4, Fig. 2.2**). Compared to CTRL, CWS had no effect on the behaviour of dynamic inspiratory reserve volume during exercise (**Fig. 2.2**), indicating that CWS-induced reductions in V_T expansion reflected simultaneous reductions in dynamic IC. Mean values of EMGdi,rms and peak expiratory Pga were higher, while tidal Pes and Pdi swings were not different during submaximal exercise with vs. without CWS (**Table 2.4, Fig. 2.3**). Compared with placebo, nebulized fentanyl had no effect on EET or the integrated physiological response to exercise with and/or without CWS (**Tables 2.3 & 2.4, Figs. 2.2 & 2.3**).

Symptom responses. Intensity ratings of leg discomfort were different at end-exercise only with vs. without CWS (**Tables 2.3 & 2.4**). Intensity and unpleasantness ratings of dyspnea were much higher throughout exercise with vs. without CWS (**Tables 2.3 & 2.4, Fig. 2.4**). Compared with CTRL, CWS increased the percentage contribution of intolerable dyspnea and decreased the percentage of intolerable leg discomfort to exercise cessation (**Table 2.3**). Similarly, the locus of symptom-limitation shifted away from intolerable leg discomfort to intolerable dyspnea during exercise with vs. without CWS (**Appendix A**). Compared with CTRL, CWS increased the selection frequency of qualitative descriptor phrases alluding to a heightened sense of 'unsatisfied inspiration' (e.g., 'I cannot get enough air in') at end-exercise by 2-3 fold

(**Appendix B**). Compared with placebo, nebulized fentanyl had no effect on symptom ratings during exercise with and/or without CWS (**Tables 2.3 & 2.4, Fig. 2.4**).

Table 2.2. Effects of chest wall strapping, nebulized fentanyl citrate (250 µg) and their interaction on pulmonary function test parameters.

	Control		Chest Wall Strapping		P value		
Parameter	**Placebo**	**Fentanyl Citrate**	**Placebo**	**Fentanyl Citrate**	**Condition (CTRL vs. CWS)**	**Treatment (PLA vs. FC)**	**Condition * Treatment**
SVC, L	5.15 ± 0.15	5.12 ± 0.15	4.16 ± 0.14	4.16 ± 0.14	<0.001	0.636	0.557
FVC, L	5.04 ± 0.14	4.98 ± 0.15	4.10 ± 0.13	4.16 ± 0.16	<0.001	0.982	0.229
FEV_1, L	4.13 ± 0.15	4.29 ± 0.15	3.37 ± 0.13	3.40 ± 0.14	<0.001	0.355	0.368
FEV_1/FVC, %	82.0 ± 2.0	81.9 ± 2.1	82.1 ± 1.8	82.0 ± 1.8	0.908	0.851	0.945
PEFR, L/sec	9.35 ± 0.41	9.22 ± 0.46	8.37 ± 0.35	8.34 ± 0.41	<0.001	0.735	0.796
$FEF_{25-75\%}$, L/sec	4.29 ± 0.33	4.31 ± 0.37	3.51 ± 0.25	3.48 ± 0.25	<0.001	0.994	0.724

Values are means ± SEM. CTRL, unrestricted control; CWS, chest wall strapping; PLA, placebo; FC, fentanyl citrate; SVC, slow vital capacity; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1-sec; PEFR, peak expiratory flow rate; $FEF_{25-75\%}$, forced expiratory flow between 25% and 75% of the FVC maneuver.

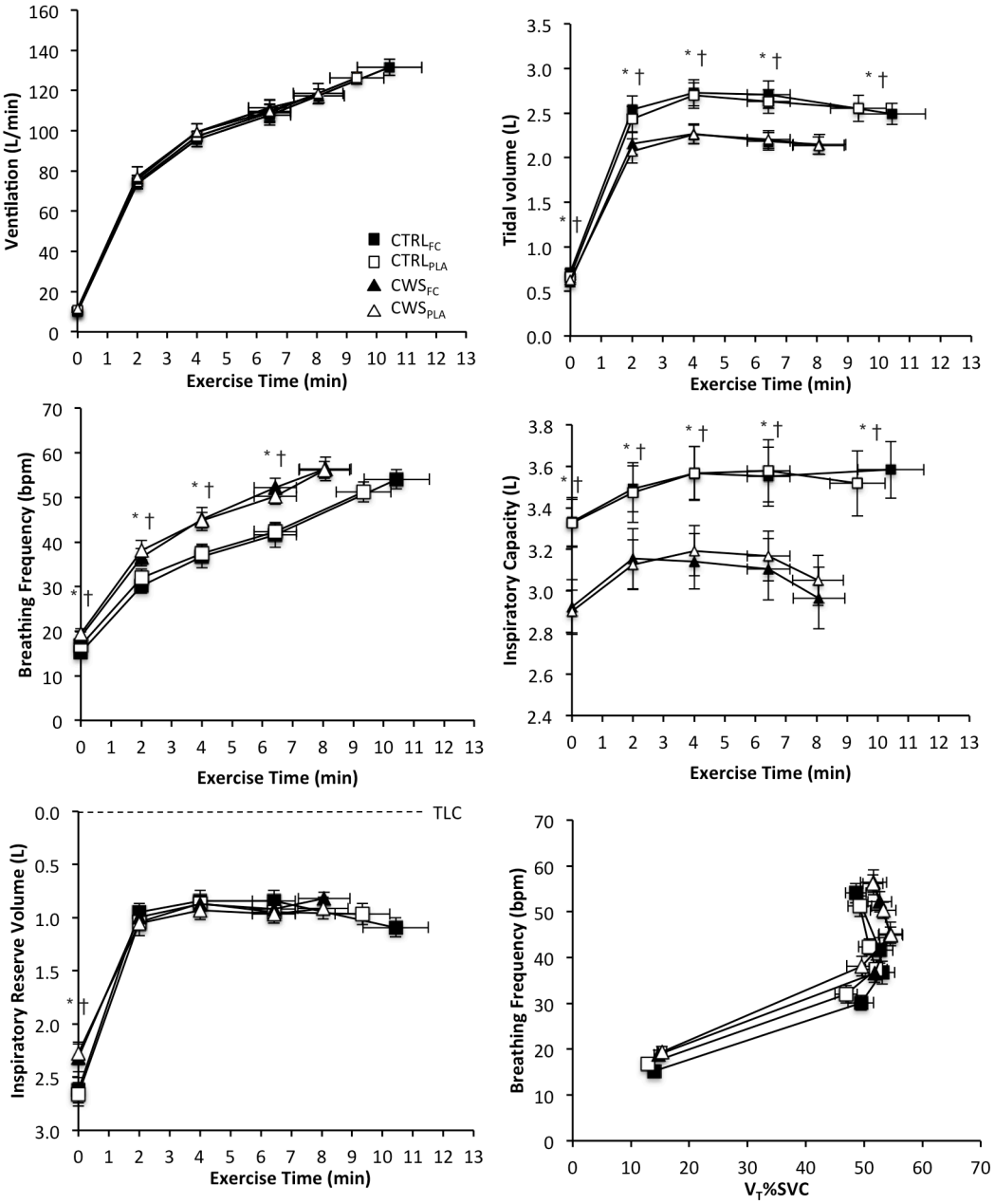

Fig. 2.2. Effects of chest wall strapping, nebulized fentanyl citrate (250 µg) and their interaction on ventilatory, breathing pattern and operating lung volume responses to constant work rate cycle exercise performed at 85% of maximal incremental work rate, equivalent to 204 ± 10 watts. Data points are means ± SEM at rest, standard submaximal exercise time points including isotime (6.4 ± 0.7 min), and at peak exercise. $CTRL_{FC}$, unrestricted control + nebulized fentanyl citrate; $CTRL_{PLA}$, unrestricted control + nebulized placebo; CWS_{FC}, chest wall strapping + nebulized fentanyl citrate; CWS_{PLA}, chest wall strapping + nebulized placebo; TLC, total lung capacity; V_T, tidal volume; SVC, slow vital capacity. *p<0.05 CWS_{PLA} vs. $CTRL_{PLA}$. †p<0.05 CWS_{FC} vs. $CTRL_{FC}$.

Table 2.3. Effects of chest wall strapping, nebulized fentanyl citrate (250 µg) and their interaction on physiological and symptom responses at the symptom-limited peak of constant work rate cycle exercise performed at 85% *W*max.

	Control		Chest Wall Strapping		P value		
Parameter	**Placebo**	**Fentanyl Citrate**	**Placebo**	**Fentanyl Citrate**	**Condition (CTRL vs. CWS)**	**Treatment (PLA vs. FC)**	**Condition * Treatment**
Exercise endurance time, min	9.3 ± 0.9	10.4 ± 1.1	8.0 ± 0.8	8.1 ± 0.9	0.003	0.264	0.205
$V'O_2$, mL/kg/min	55.5 ± 2.3	56.6±2.1	55.1±2.5	56.1±2.6	0.559	0.094	0.924
Heart rate, beats/min	184.9 ± 1.7	186.8 ± 1.9	183.9 ± 1.8	183.4 ± 2.2	0.259	0.621	0.553
O_2 pulse, mL O_2/beat	20.8 ± 0.9	21.0 ± 0.9	20.8 ± 1.1	21.0 ± 0.8	0.786	0.420	0.957
$V'_E/V'CO_2$	36.1 ± 1.0	36.2 ± 0.9	33.4 ± 0.8	32.7 ± 1.0	<0.001	0.531	0.277
$P_{ET}CO_2$, mmHg	31.2 ± 0.8	32.1 ± 1.2	33.6 ± 0.9	34.2 ± 0.8	0.011	0.135	0.764
V'_E, L/min	126.1 ± 3.0	131.4 ± 4.0	118.5 ± 5.12	117.3 ± 3.4	0.001	0.237	0.129
V_T, L	2.55 ± 0.15	2.49 ± 0.12	2.14 ± 0.10	2.15 ± 0.11	<0.001	0.522	0.438
V_T, %SVC	49.3 ± 2.0	48.6 ± 1.8	51.5 ± 1.7	51.6 ± 2.2	0.064	0.773	0.656
f_R, bpm	51.2 ± 2.2	54.1 ± 2.1	56.2 ± 1.9	56.4 ± 2.7	0.083	0.208	0.380
IC, L	3.52 ± 0.16	3.58 ± 0.14	3.05 ± 0.12	2.96 ± 0.15	<0.001	0.915	0.367
IC, %SVC	68.1 ± 1.8	70.0 ± 1.7	73.8 ± 2.5	71.2 ± 2.4	0.089	0.860	0.251
Δ IC from rest, L	0.19 ± 0.08	0.25 ± 0.05	0.15 ± 0.07	0.05 ± 0.10	0.091	0.763	0.236
IRV, L	0.97 ± 0.10	1.09 ± 0.09	0.91 ± 0.10	0.82 ± 0.06	0.089	0.826	0.081
IRV, %SVC	19.3 ± 2.1	22.1 ± 1.8	22.8 ± 2.7	19.5 ± 1.1	0.657	0.952	0.076
T_I, sec	0.61 ± 0.03	0.57 ± 0.02	0.55 ± 0.02	0.56 ± 0.02	0.188	0.163	0.214
T_E, sec	0.60 ± 0.03	0.58 ± 0.03	0.54 ± 0.02	0.55 ± 0.03	0.079	0.384	0.204
EMGdi,rms, µV	131.0 ± 12.9	146.0 ± 14.1	148.5 ± 10.9	151.3 ± 14.5	0.109	0.253	0.490
Tidal Pes swing, cmH_2O	31.9 ± 3.6	35.7 ± 4.0	30.0 ± 3.9	29.4 ± 3.5	0.013	0.451	0.097
Tidal Pdi swing, cmH_2O	20.5 ± 1.9	21.8 ± 1.9	20.5 ± 1.9	20.4 ± 2.3	0.551	0.640	0.345
Peak expiratory Pga, cmH_2O	22.5 ± 2.0	26.9 ± 2.6	26.3 ± 2.8	26.4 ± 3.1	0.340	0.132	0.040
Dyspnea Intensity, Borg 0-10 scale units	7.1 ± 0.6	7.4 ± 0.7	8.6 ± 0.4	8.9 ± 0.5	0.011	0.419	1.000
Dyspnea Unpleasantness, Borg 0-10 scale units	5.7 ± 0.7	6.2 ± 0.7	8.8 ± 0.4	8.5 ± 0.6	<0.001	0.766	0.178
Leg Discomfort, Borg 0-10 scale units	9.3 ± 0.3	9.0 ± 0.5	8.0 ± 0.5	7.9 ± 0.6	0.017	0.606	0.879
% contribution of dyspnea to exercise cessation	21.8 ± 3.8	32.9 ± 6.3	57.5 ± 4.1	59.3 ± 7.7	<0.001	0.248	0.281
% contribution of leg discomfort to exercise cessation	78.2 ± 3.8	63.6 ± 6.8	42.5 ± 4.1	36.4 ± 7.5	<0.001	0.083	0.302

Values are means ± SEM. *W*max, maximum incremental cycle work rate; CTRL, unrestricted control; CWS, chest wall strapping; PLA, placebo; FC, fentanyl citrate; $V'O_2$, rate of oxygen consumption; $V'_E/V'CO_2$, ventilatory equivalent for carbon dioxide; $P_{ET}CO_2$, end-tidal partial pressure of carbon dioxide; V'_E, minute ventilation; V_T, tidal volume; SVC, slow vital capacity; f_R, breathing frequency; IC, inspiratory capacity; Δ, change; IRV, inspiratory reserve volume; T_I & T_E, inspiratory and expiratory time, respectively; EMGdi,rms, root mean square of the diaphragm electromyogram; Pes, Pdi and Pga, esophageal, transdiaphragmatic and gastric pressure, respectively. Tidal swings in Pes and Pdi were calculated as the difference between peak tidal inspiratory and expiratory Pes and Pdi, respectively.

Table 2.4. Effects of chest wall strapping, nebulized fentanyl citrate (250 µg) and their interaction on physiological and symptom responses at isotime (6.4 ± 0.7 min) during constant work rate cycle exercise performed at 85% *W*max.

	Control		Chest Wall Strapping		P value		
Parameter	**Placebo**	**Fentanyl Citrate**	**Placebo**	**Fentanyl Citrate**	**Condition (CTRL vs. CWS)**	**Treatment (PLA vs. FC)**	**Condition * Treatment**
$V'O_2$, mL/kg/min	52.5 ± 2.6	52.4 ± 2.4	52.5 ± 2.9	54.4 ± 2.8	0.155	0.108	0.154
Heart rate, beats/min	176.6 ± 2.0	178.0 ± 2.3	178.4 ± 1.7	178.6 ± 2.1	0.441	0.443	0.710
O_2 pulse, mL O_2/beat	20.6 ± 1.0	20.4 ± 1.0	20.36 ± 1.2	21.06 ± 1.1	0.242	0.132	0.105
$V'_E/V'CO_2$	31.2 ± 0.8	30.2 ± 1.0	31.20 ± 0.9	30.8 ± 0.7	0.560	0.196	0.387
$P_{ET}CO_2$, mmHg	35.4 ± 0.9	36.8 ± 1.1	35.8 ± 1.1	35.8 ± 0.7	0.627	0.238	0.141
V'_E, L/min	109.0 ± 4.3	107.9 ± 5.1	109.6 ± 5.6	111.3 ± 4.1	0.472	0.904	0.575
V_T, L	2.63 ± 0.13	2.71 ± 0.16	2.20 ± 0.10	2.18 ± 0.10	<0.001	0.467	0.208
V_T, %SVC	50.9 ± 1.8	52.67 ± 2.3	53.3 ± 2.2	52.7 ± 2.1	0.286	0.565	0.242
$f_{R,}$ bpm	42.4 ± 1.8	41.6 ± 2.8	50.3 ± 1.8	52.1 ± 2.2	<0.001	0.739	0.400
IC, L	3.58 ± 0.15	3.55 ± 0.14	3.17 ± 0.12	3.10 ± 0.15	<0.001	0.552	0.812
Δ IC from rest, L	0.25 ± 0.09	0.22 ± 0.06	0.27 ± 0.09	0.19 ± 0.12	0.919	0.383	0.742
IC, %SVC	69.4 ± 1.9	69.3 ± 1.7	76.5 ± 2.1	74.8 ± 2.8	0.005	0.575	0.636
IRV, L	0.95 ± 0.07	0.84 ± 0.10	0.97 ± 0.09	0.92 ± 0.06	0.592	0.170	0.630
IRV %SVC	18.6 ± 1.4	16.7 ± 2.0	23.2 ± 2.0	22.1 ± 1.2	0.009	0.185	0.788
T_I, sec	0.73 ± 0.04	0.76 ± 0.05	0.64 ± 0.04	0.59 ± 0.03	0.002	0.662	0.065
T_E, sec	0.73 ± 0.04	0.77 ± 0.05	0.60 ± 0.02	0.60 ± 0.03	<0.001	0.495	0.192
EMGdi,rms, µV	118.0 ± 11.0	126.6 ± 11.6	139.3 ± 10.0	139.2 ± 13.2	0.029	0.296	0.387
Tidal Pes swing, cmH_2O	26.9 ± 3.2	26.1 ± 2.5	26.4 ± 3.6	27.3 ± 3.7	0.774	0.940	0.297
Tidal Pdi swing, cmH_2O	21.1 ± 2.5	19.6 ± 1.5	21.5 ± 2.2	20.6 ± 2.4	0.561	0.433	0.792
Peak expiratory Pga, cmH_2O	20.9 ± 1.9	19.8 ± 1.9	26.3 ± 2.7	25.7 ± 2.9	0.006	0.533	0.743
Dyspnea Intensity, Borg 0-10 scale units	4.6 ± 0.5	4.4 ± 0.5	7.3 ± 0.5	7.5 ± 0.6	<0.001	1.000	0.321
Dyspnea Unpleasantness, Borg 0-10 scale units	3.7 ± 0.5	3.2 ± 0.6	7.4 ± 0.6	7.1 ± 0.6	<0.001	0.352	0.716
Leg Discomfort, Borg 0-10 scale units	6.9 ± 0.5	5.9 ± 0.5	7.1 ± 0.5	6.6 ± 0.6	0.239	0.152	0.439

Values are means ± SEM. *W*max, maximum incremental cycle work rate; CTRL, unrestricted control; CWS, chest wall strapping; PLA, placebo; FC, fentanyl citrate; $V'O_2$, rate of oxygen consumption; $V'_E/V'CO_2$, ventilatory equivalent for carbon dioxide; $P_{ET}CO_2$, end-tidal partial pressure of carbon dioxide; V'_E, minute ventilation; V_T, tidal volume; SVC, slow vital capacity; f_R, breathing frequency; IC, inspiratory capacity; Δ, change; IRV, inspiratory reserve volume; T_I & T_E, inspiratory and expiratory time, respectively; EMGdi,rms, root mean square of the diaphragm electromyogram; Pes, Pdi and Pga, esophageal, transdiaphragmatic and gastric pressure, respectively. Tidal swings in Pes and Pdi were calculated as the difference between peak tidal inspiratory and expiratory Pes and Pdi, respectively.

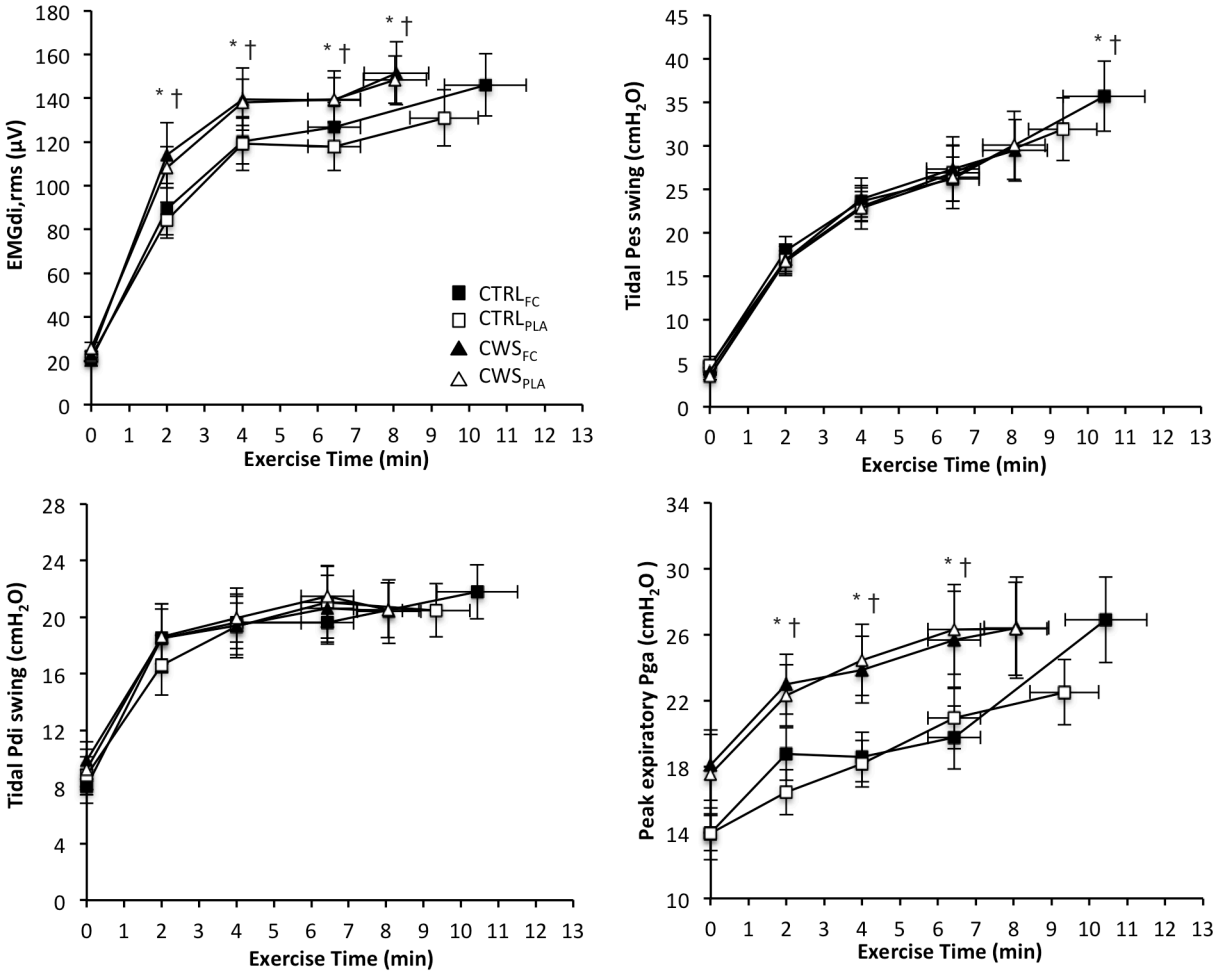

Fig. 2.3. Effects of chest wall strapping, nebulized fentanyl citrate (250 μg) and their interaction on neural respiratory drive and respiratory pressures during constant work rate cycle exercise performed at 85% of maximal incremental work rate, equivalent to 204 ± 10 watts. Data points are means ± SEM at rest, standard submaximal exercise time points including isotime (6.4 ± 0.7 min), and at peak exercise. $CTRL_{FC}$, unrestricted control + nebulized fentanyl citrate; $CTRL_{PLA}$, unrestricted control + nebulized placebo; CWS_{FC}, chest wall strapping + nebulized fentanyl citrate; CWS_{PLA}, chest wall strapping + nebulized placebo. EMGdi,rms, root mean square of the diaphragm electromyogram; Pes, esophageal pressure; Pdi, transdiaphragmatic pressure; Pga, gastric pressure. *p<0.05 CWS_{PLA} vs. $CTRL_{PLA}$. †p<0.05 CWS_{FC} vs. $CTRL_{FC}$.

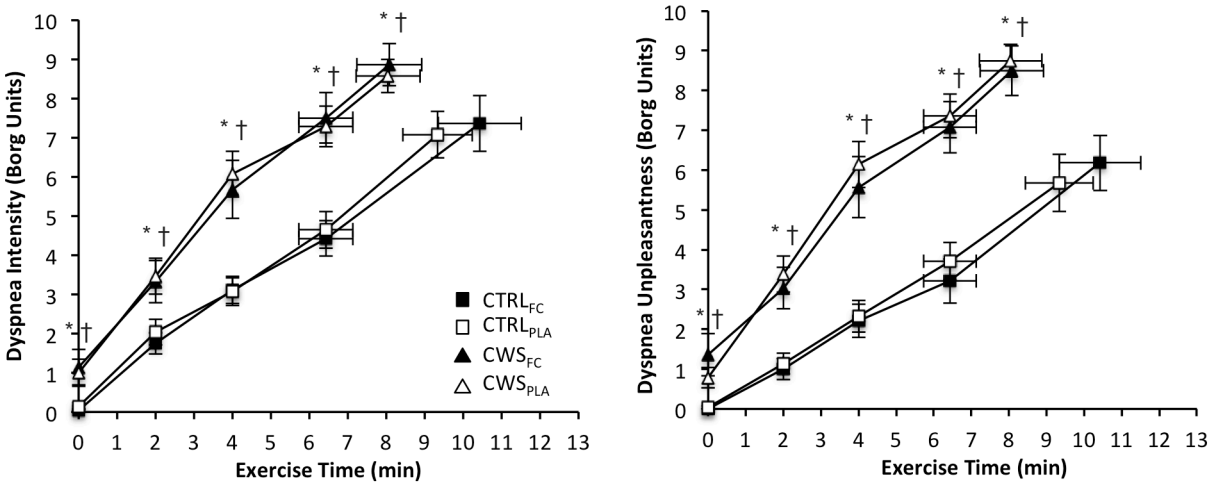

Fig. 2.4. Effects of chest wall strapping, nebulized fentanyl citrate (250 µg) and their interaction on Borg 0-10 scale intensity and unpleasantness ratings of dyspnea during constant work rate cycle exercise performed at 85% of maximal incremental work rate, equivalent to 204 ± 10 watts. Data points are means ± SEM at rest, standard submaximal exercise time points including isotime (6.4 ± 0.7 min), and at peak exercise. $CTRL_{FC}$, unrestricted control + nebulized fentanyl citrate; $CTRL_{PLA}$, unrestricted control + nebulized placebo; CWS_{FC}, chest wall strapping + nebulized fentanyl citrate; CWS_{PLA}, chest wall strapping + nebulized placebo. *p<0.05 CWS_{PLA} vs. $CTRL_{PLA}$. †p<0.05 CWS_{FC} vs. $CTRL_{FC}$.

2.5. Discussion

The primary finding of our randomized, double-blind, placebo-controlled cross-over study is that single-dose inhalation of nebulized fentanyl citrate (250 μg) had no effect on exertional dyspnea, exercise tolerance or the integrated physiological response to exercise with and without external thoracic restriction in healthy man.

Although systemic opioids are a safe and effective intervention for the management of dyspnea in cardiopulmonary disease [49, 149, 150], many healthcare providers remain skeptical of their use for fear of adverse side-effects [53, 54, 151]. In theory, intrapulmonary opioid receptors [56, 58, 65, 66, 135] represent a promising pharmacological target in the management of dyspnea. As reviewed in the introduction, pulmonary administration of nebulized opioids may improve dyspnea and exercise tolerance with no adverse side-effects. Indeed, a RCT by Young et al. [112] reported that the administration of nebulized morphine (0.4-2.8 mg) to 9 patients with chronic obstructive pulmonary disease (COPD) and 2 patients with pulmonary fibrosis was associated with no adverse side-effects and a significantly greater mean improvement in EET (+33%) than placebo (+4%). A RCT by Jensen et al. [152] similarly reported that, compared with placebo, nebulized fentanyl (50 μg) was associated with no adverse side-effects, a significant mean improvement (+25%) in EET, and a delay in the onset of intolerable dyspnea during cycle exercise near the limits of tolerance in 12 patients with COPD. In contrast to the above and our original hypothesis, the results of our study confirm and extend those of previous RCTs reporting a lack of benefit of nebulized morphine (1.0-40 mg) on dyspnea and/or exercise tolerance in health [115], ILD [122] and COPD [116-119].

Methodological considerations. External thoracic restriction in health does not accurately reproduce the intrinsic mechanical loads and/or impersonate the long-term sensory effects of RLDs. Nevertheless, CWS sufficient to decrease vital capacity by ~20% in healthy men mimicked the consequences of a 'mild' RLD on detailed physiological and perceptual responses at rest and during exercise [14, 23, 27, 41, 128] without the potentially confounding influences of co-morbidities, deconditioning, hypoxemia, etc. In this regard and in keeping with the results of earlier studies [43, 125, 126], CWS was associated with: reductions in FEV_1, mid-maximal expiratory flow rates, IC and inspiratory reserve volume at rest; relative preservation of the FEV_1/FVC ratio; reduced EET; increased dynamic mechanical ventilatory constraints, tachypnea and increased neural respiratory drive (EMGdi,rms) during exercise; a shift in the locus of symptom-limitation from leg discomfort to dyspnea; and clinically meaningful increases in the intensity [148] and unpleasantness of exertional dyspnea, which was described as a heightened sense of 'unsatisfied inspiration.'

Our study was designed so that any change in dyspnea would most likely reflect a pulmonary (peripheral) vs. central mechanism of action of nebulized fentanyl. First, Worsley et al. [153] reported that serum fentanyl levels following inhalation of 300 μg nebulized fentanyl plateaued at 0.1 ng/mL after 15-min, indicating very low systemic bioavailability. In our study, 250 μg of nebulized fentanyl was administered, while exercise tests were initiated ~45-min post-nebulization. Second, we optimized delivery of fentanyl to the airways and lungs by studying healthy men without airway obstruction/secretions [154]; administering a relatively high nebulized dose of fentanyl through a mouthpiece (vs. open facemask) during deep and slow tidal inspirations [154]; and using a nebulizer that produces particles with a mass median

diameter (~5 μm) capable of traversing the small airways and anatomical dimensions of the alveoli [155, 156]. Consistent with the results of an elegant study by Mahler et al. [121], our findings suggest that intrapulmonary opioids do not contribute to the neuromodulation of dyspnea and that the benefit of systemically administered opioids on dyspnea [49, 69, 149, 150] most likely reflects a central mechanism of action.

Exercise tests were initiated ~45-min post-nebulization; thus, the lack of effect of nebulized fentanyl on measured parameters may reflect diminution of its analgesic potency. Although information was not available for pulmonary administration, the product monograph for the fentanyl used herein reported that the duration of analgesic effect following an intravenous, intramuscular and epidural dose of up to 100 μg (vs. 250 μg in our study) is 30-60 min, 1-2 hrs and 2-5 hrs, respectively. Furthermore, studies that initiated exercise ≤30-min after nebulization of morphine also reported no benefit on dyspnea and exercise performance in health [115], ILD [122] and COPD [116, 117, 119]. Thus, diminution of fentanyl's analgesic potency at the level of the intrapulmonary μ-opioid receptors was not likely responsible for our negative results.

Fentanyl is a synthetic opioid well suited for pulmonary delivery: compared to morphine, fentanyl is more potent and lipophilic, has a shorter duration of activity, and does not cause the release of histamine. Indeed, Simon et al. [104] and Boyden et al. [124] recently indicated that, although well-designed and adequately powered efficacy trials are lacking, sufficient evidence exists to suggest a potential benefit of nebulized fentanyl for the relief of dyspnea. Unfortunately, the results of our RCT do not provide proof of efficacy of nebulized fentanyl for the relief of dyspnea, at least not in healthy men during exercise with and without

external thoracic restriction.

Although we estimated *a priori* that ≥28 participants were needed to detect a ±1 Borg unit difference in dyspnea intensity ratings at isotime among the 4 conditions, a blinded efficacy analysis of the first 14 men completing our study provided no clear evidence of a potentially significant and/or meaningful treatment effect or treatment*condition interaction on our primary outcome variable (**Table 2.4**). As such, our trial was ceased (for ethical reasons) after testing 50% of our pre-determined minimum sample size. Thus, we cannot preclude the possibility that a Type II statistical error is responsible, at least in part, for our negative results.

2.6. Conclusions

Our findings do not support a role of intrapulmonary opioids in modulating the symptom of dyspnea during exercise in health nor do they provide a physiological rationale for further examination of nebulized fentanyl in the management of exertional dyspnea in restrictive lung disorders, particularly those arising from disorders of the chest wall (e.g., kyphoscoliosis, pectus excavatum) and not affiliated with airway inflammation.

CHAPTER THREE. CONCLUDING REMARKS

3.1. Summary

The general aim of this M.Sc. thesis was to examine the potential benefits of high-dose nebulized fentanyl on ratings of perceived dyspnea during strenuous exercise in healthy men with and without external thoracic restriction sufficient to mimic a 'mild' RLD. As discussed in *Chapter 2*, the major finding from this randomized controlled study is that, compared with placebo, single-dose nebulized fentanyl had no demonstrable effect on ratings of perceived dyspnea during constant work rate cycle exercise testing with and without external thoracic restriction. In contrast to our *a priori* hypothesis, these findings do not support a role of intrapulmonary opioids in the neuromodulation of exertional dyspnea nor do they provide a physiological rationale for further examination of nebulized fentanyl in the management of exertional dyspnea in RLDs, particularly those arising from disorders of the chest wall (e.g., kyphoscoliosis, pectus excavatum) and not affiliated with airway inflammation.

3.2. Is chest wall strapping in health an appropriate model to study the potential therapeutic benefits of nebulized opioids on exertional dyspnea?

The question arises whether external thoracic restriction by CWS in healthy men is an appropriate experimental model to study the potential therapeutic benefits of nebulized opioids on exertional dyspnea in patients with chronic pulmonary disease. In our study as well as in previous studies [14, 43, 157], CWS successfully mimicked the static and dynamic respiratory mechanical abnormalities (and their physiological and sensory consequences) commonly seen in persons with RLDs [14, 158, 159] and, to a lesser extent, in patients with chronic obstructive pulmonary disorders [113, 158, 159]. Furthermore, studying healthy adults provided access to a larger pool of potential participants, and it helped to circumvent the

potentially confounding influences of 'other' dyspneogenic stimuli (e.g., anxiety, decondition, cardiometabolic impairment, concomitant medication use) commonly encountered in patient populations. Finally, by studying healthy adults without chronic airways inflammation/obstruction/secretions, we presumably optimized the delivery of nebulized fentanyl to the μ-opioid receptors located throughout the tracheobronchial tree and in the alveoli.

Notwithstanding these advantages, certain limitations of using the CWS-model in healthy adults certainly exist and warrant consideration. First, CWS in health only mimics diseases of the chest wall such as kyphoscoliosis and pectus excavatum. In this regard, CWS imprecisely simulates the chronic intrinsic mechanical loading of the respiratory system characteristic of many RLDs (namely ILD) and does not replicate the chronic inflammatory aspect of chronic airway diseases commonly associated with activity-related dyspnea (e.g., COPD) [125, 157]. Additionally, as discussed in detail in *Section 1.9*, clinical and experimental observations suggest that the analgesic potency of opioids is increased in the presence of tissue inflammation and injury [91]. Indeed, available evidence suggests that tissue inflammation and damage up-regulate the synthesis, expression, sensitivity and axonal transport of μ-opioid receptors toward the peripheral sensory nerve endings, including those in the airways, i.e., bronchopulmonary C-fibers and pulmonary neuroendocrine cells [61, 90, 91]. Inflammation has also been shown to cause disruption of the perineural sheath thus increasing, at least in theory, the accessibility of inhaled μ-opioid receptor agonists (e.g., morphine, fentanyl) to their corresponding receptor subtype [61, 93]. These compensatory adaptations to tissue inflammation and damage are thought to facilitate the homeostatic regulation of peripheral

inflammation by attenuating the excitability of peripheral sensory nerves to endogenous and perhaps also exogenous opioids [61, 97]. Indeed, *in vitro* studies have shown an inhibitory effect of μ-opioids on factors known to contribute to chronic inflammatory airway disease, namely neurogenic mucus hypersecretion [94], goblet cell secretion [96] and plasma extravasation [94, 95].

The possibility therefore remains that the lack of benefit of nebulized fentanyl citrate on exertional dyspnea in our study may be explained, at least in part, by inclusion of apparently healthy men with normal spirometry (**Table 2.1**) who, unlike many patients with chronic pulmonary disease, neither suffered from troublesome activity-related dyspnea nor had a known or suspected history of chronic inflammatory airway disease. In other words, intrapulmonary μ-opioid receptors may not have been particularly sensitive, abundant and/or accessible to the analgesic effect(s) of nebulized fentanyl citrate in our participants.

In light of the information cited above, it is reasonable to postulate that the potential benefits of nebulized opioids on dyspnea and exercise tolerance may only present themselves in symptomatic patients with chronic inflammatory airways disease. In keeping with the results of numerous case-control studies and anecdotal reports [107-111], Jensen et al. [160] and Young et al. [112] showed positive effects of low-dose nebulized fentanyl and morphine, respectively, on exercise endurance in symptomatic patients with COPD. By contrast, numerous other randomized controlled studies, including the one presented here, have failed to provide proof of efficacy of nebulized opioids for the relief of exertional dyspnea in patients with ILD and COPD [116, 117, 119, 122].

The reason(s) for the inconsistencies in the literature concerning the influence of nebulized opioids on exertional dyspnea and exercise tolerance in health and disease remain unclear and highly conjectural [59, 61, 91, 161]. Even though the majority of available evidence does not support a role for intrapulmonary opioids in the neuromodulation of exertional dyspnea in health and disease [102, 104, 124, 162], there nevertheless remains a reasonably strong physiological rationale for the use of nebulized opioids in the management of dyspnea in chronic inflammatory airways disease[59] (refer to *Sections 1.9 and 2.5*) and published studies have not yet provided definitive answers to the following questions:

1) Are nebulized opioids an effective adjunct intervention for the relief of exertional dyspnea in selected patients with chronic pulmonary disorders receiving optimal medical therapy?
2) Are some patients more likely to benefit from nebulized opioids than others and, if so, why? In other words, is there a nebulized opioid responder phenotype?
3) Is there a benefit of longer-term (vs. short-term) use of nebulized opioids on exertional symptoms in patients with chronic pulmonary disorders? If yes, is longer-term use of nebulized opioids safe and devoid of side effects?
4) What is the optimal dose and the most effective mode of delivering opioid drugs to the intrapulmonary opioid receptors?
5) Does the effect of nebulized opioids on dyspnea depend, at least in part, on the choice of μ-opioid agonist used?

To address these lingering questions, future studies should examine the acute and chronic effect of low, medium and high-dose nebulized opioids on exercise physiological and perceptual responses in large, diverse and well-characterized cohorts of symptomatic and asymptomatic

men and women with mild-to-very severe chronic cardiopulmonary disorders. In addition to the detailed psycho-physiological assessments performed at rest and during exercise in the present study, these future studies should include: a variety of μ-opioid agonists and drug delivery systems; more sensitive tests of small airway function (e.g., plethysmography, impulse oscillometry); blood sampling for the determination of circulating opioid concentrations and systemic inflammatory biomarkers; and detailed assessment of airway and lung specific inflammatory biomarkers.

3.3. Concluding Remarks

The results of the studies outlined in this M.Sc. thesis have advanced our understanding of the neurobiology of exertional dyspnea, which is important for identifying and/or developing more effective treatments for this distressing and disabling symptom in the clinical setting. In particular, the collective results of our studies do not support a role of intrapulmonary opioids in the neurobiology of exertional dyspnea (at least not in healthy young men) nor do they provide a physiological rationale for future scrutiny of nebulized opioids in the pharmacological management of exertional dyspnea due to restrictive lung disorders, particularly those arising from diseases of the chest wall and not associated with chronic airway inflammation. Although the results of our studies were negative, the methodology was unique and illustrates how the combination of cardiopulmonary cycle exercise testing (with detailed assessments of diaphragmatic EMG and respiratory pressures) and chest wall strapping in healthy adults may serve as a useful model to (1) assess the efficacy of potential therapies for exertional dyspnea

before clinical trials in patients with restrictive lung disorders and (2) elucidate the physiological mechanism(s) that may underlie dyspnea relief with these therapies.

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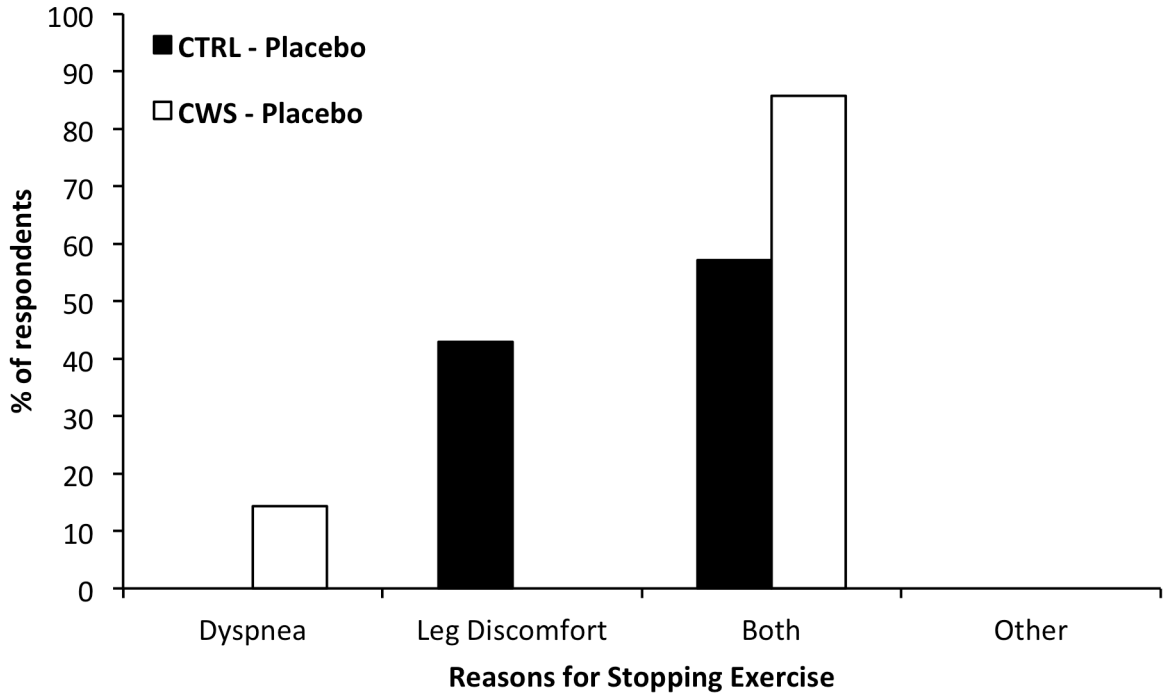
APPENDIX A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% of respondents
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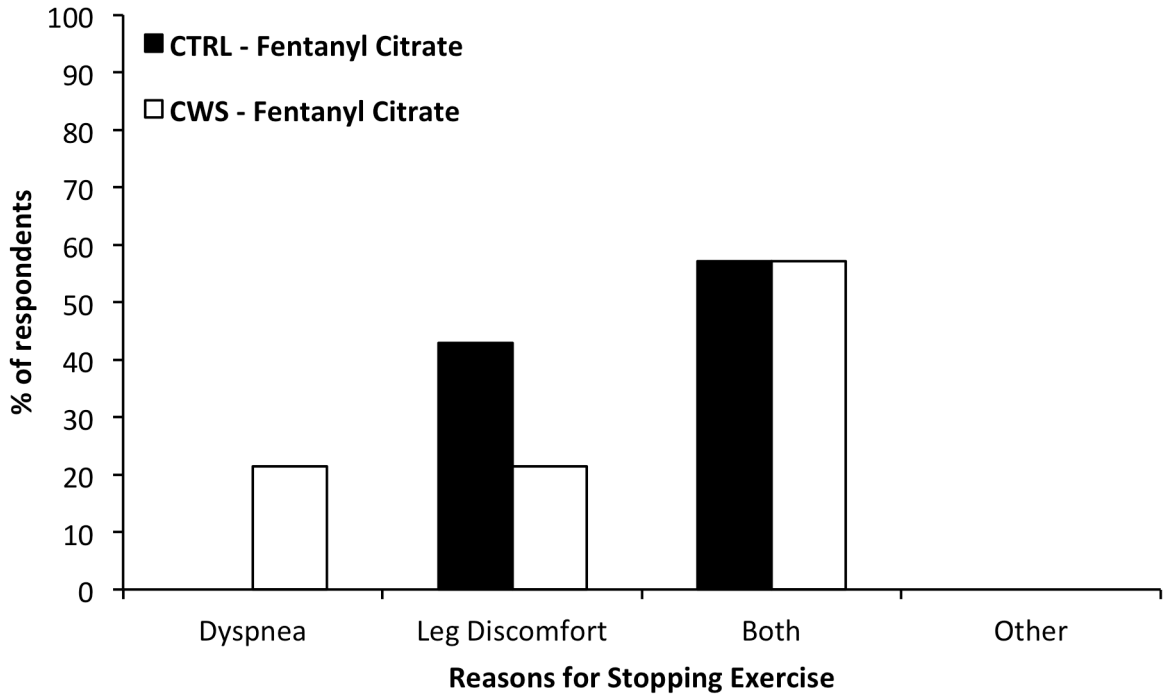
CWS - Placebo
Dyspnea
Leg Discomfort
Both
Other
Reasons for Stopping Exercise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Leg Discomfort
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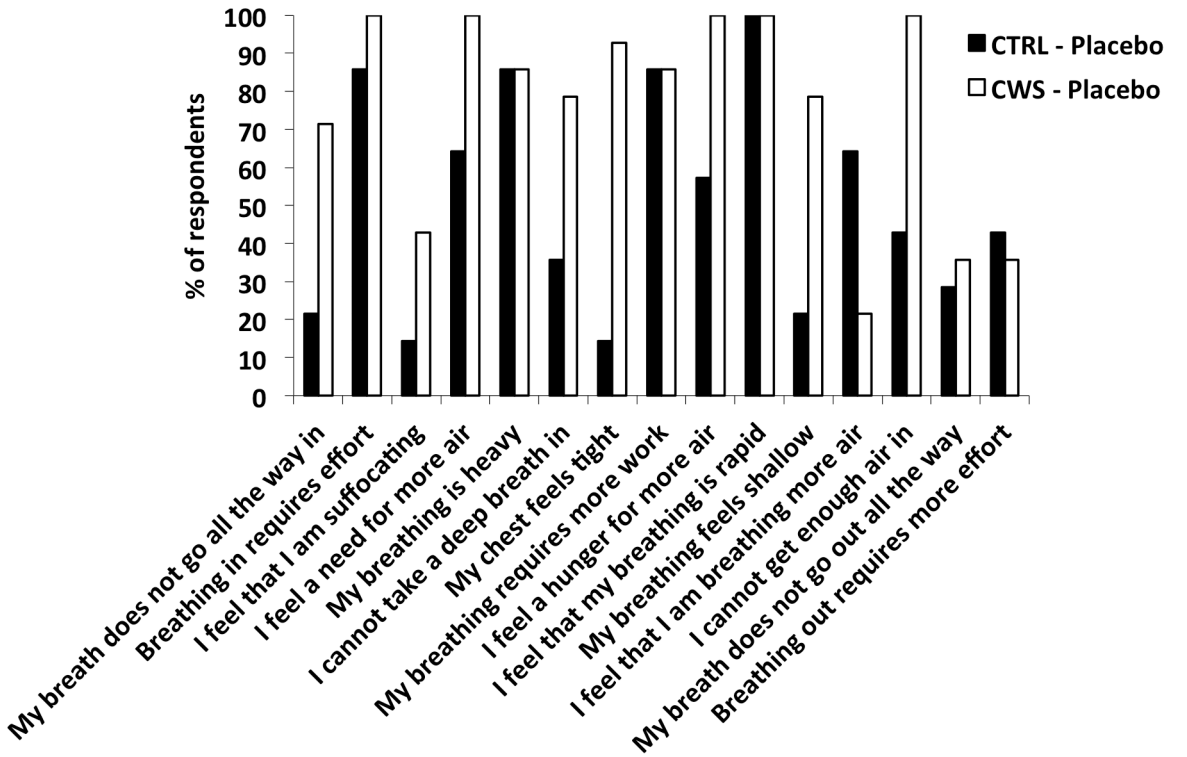
Reasons for Stopping Exercise

APPENDIX B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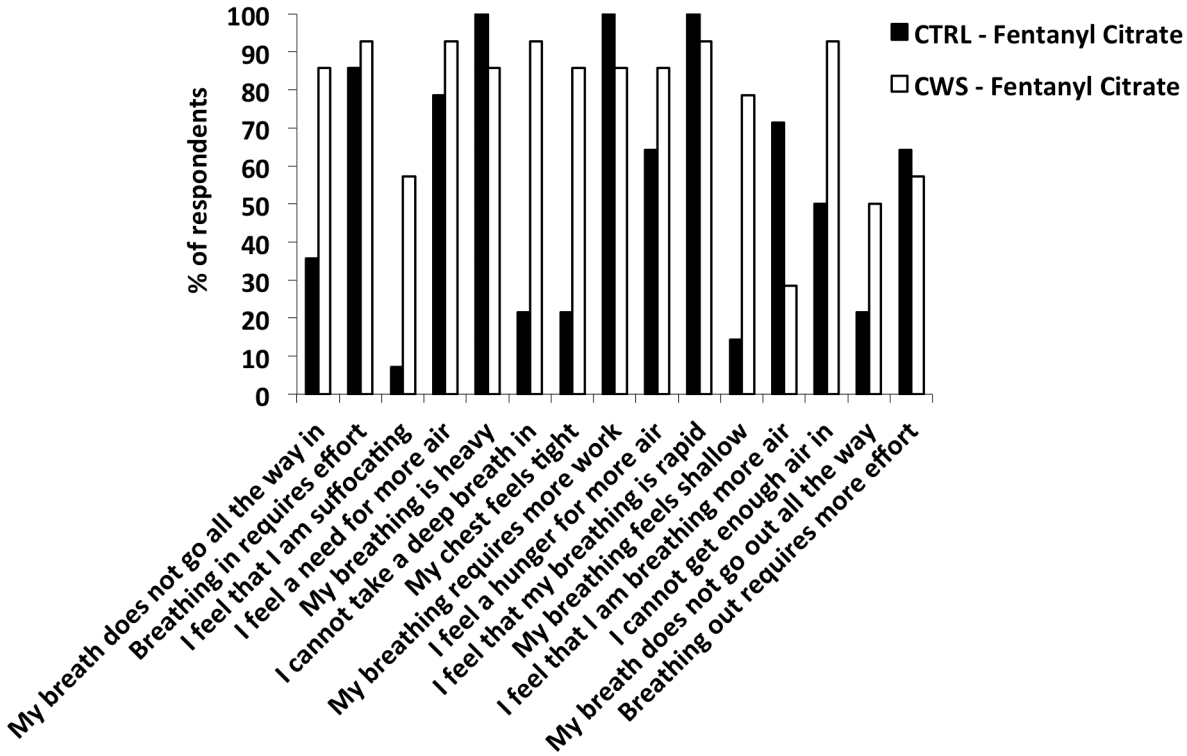
CTRL - Placebo
CWS - Placebo
My breath does not go all the way in
Breathing in requires effort
I feel that I am suffocating
I feel a need for more air
My breathing is heavy
I cannot take a deep breath in
My chest feels tight
My breathing requires more work
I feel a hunger for more air
I feel that my breathing is rapid
My breathing feels shallow
I feel that I am breathing more air
I cannot get enough air in
My breath does not go out all the way
Breathing out requires more effort


% of respondents
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CTRL - Fentanyl Citrate
CWS - Fentanyl Citrate
My breath does not go all the way in
Breathing in requires effort
I feel that I am suffocating
I feel a need for more air
My breathing is heavy
I cannot take a deep breath in
My chest feels tight
My breathing requires more work
I feel a hunger for more air
I feel that my breathing is rapid
My breathing feels shallow
I feel that I am breathing more air
I cannot get enough air in
My breath does not go out all the way
Breathing out requires more effort