SPIROMETRICALLY DEFINED RESTRICTIVE lung impairment is common in the general population, with a prevalence ranging from 12.7 to 14.2% (40, 68, 72). It is well established that the clinical manifestations of restrictive lung disorders (RLDs), namely dyspnea and activity limitation (23, 27, 41, 43, 50), have an adverse effect on health status and quality of life (19, 20, 27, 62, 71). It follows that alleviating dyspnea and improving exercise tolerance are among the principal goals in the management of RLDs (36, 39, 63). With the exception of pulmonary rehabilitation (26), few therapeutic options exist for the management of exertional symptoms in RLDs.

On the basis of our current understanding of the neurophysiology of exertional dyspnea (16, 30, 52, 54) and the collective results of numerous in vitro studies (7, 9, 11, 15, 21, 32, 55), there are reasons to believe that inhalation of nebulized opioids selective for the mu-receptor subtype may relieve dyspnea during exercise by altering the activity of opioid receptors located in the tracheobronchial tree and alveoli (12, 17, 18, 31, 33, 76, 77, 81). From a clinical perspective, inhaled opioids are attractive because this route of opioid administration is the most accepted/preferred among patients with dyspnea (67) and may be associated with no adverse side effects (8) that have limited the widespread use of systemic opioids for relief of dyspnea (22, 59, 79). Nevertheless, only one randomized controlled trial has examined the effect of nebulized morphine (2.5 and 5.0 mg) on exertional dyspnea and incremental cycle exercise capacity in six patients with RLD: three with pulmonary fibrosis; two with scleroderma; and one with sarcoidosis (24). Compared with 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., comorbidities, deconditioning, hypoxemia), and the relatively low doses of morphine used or employment of incremental exercise tests (or both), which are less responsive than constant work rate tests for evaluating the efficacy of a therapeutic intervention on dyspnea and exercise tolerance (53).

The purpose of our randomized controlled trial was first to test the hypothesis that single-dose inhalation of nebulized fentanyl (a synthetic mu-opioid receptor agonist that is more potent and lipophilic than morphine and thus well-suited for pulmonary delivery) relieves dyspnea and improves exercise tolerance during exercise in the presence of abnormal restrictive ventilatory constraints and, second, to identify the one or more physiological mechanisms underlying these improvements. To this end, we examined the effect of nebulized fentanyl (250 μg), external thoracic restriction sufficient to mimic a mild RLD (46), and their interaction on detailed assessments of dyspnea (sensory intensity and affective dimensions), ventilation, breathing pattern, dynamic operating lung volumes, diaphragmatic electromyography (EMG) and dynamic respiratory muscle function during constant work rate cycle exercise testing in healthy, young men.

METHODS

Randomized, double-blind, placebo-controlled study design. After providing informed consent, healthy men aged 20-40 yr with normal spirometry (74) recruited by word of mouth and advertisements participated in five testing visits. Visit 1 included pulmonary function tests and an incremental cycle exercise test to determine maximal work rate (Wmax). During Visits 2–5, participants completed a modified version of the Opioid-Related Symptom Distress Scale
and unpleasantness of their breathing. At end-exercise, participants verbalized their main reason or reasons for stopping exercise, quantified the percentage contribution of breathing and leg discomfort to exercise cessation, and identified qualitative phrases that described their breathing at end-exercise (51).

**Analysis of exercise end points.** All physiological parameters were averaged over the first 30 s of every second minute during exercise and linked with symptom ratings and IC measurements collected during the last 30 s of the same minute. Measured parameters were evaluated at three main time points: rest was the average of the last 30 s of the steady-state period after ≥2 min of breathing on the mouthpiece before exercise; isotime was the average of the last 30 s of the highest equivalent 2-min stage of CWR exercise completed by a given participant; and peak exercise was the average of the last 30 s of loaded pedaling, while exercise endurance time was the duration of loaded pedaling.

**Data analysis.** Using a Web-based power/sample size calculator (37), we estimated that 28 participants would provide >80% power to detect a ±1 Borg 0–10 scale unit difference (58) in our primary outcome variable (dyspnea intensity at isotime) among the four 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 exertional dyspnea was defined as “the global awareness of your breathing,” which is consistent with the American Thoracic Society’s most recent recommendation that “the definition of dyspnea should be neutral with respect to any particular quality” of breathing (54). Leg discomfort was defined as “the difficulty associated with pedaling.” Prior to each exercise test, participants were familiarized with the Borg scale and its end points were anchored such that 0 represented “no intensity (unpleasantness) you have ever experienced or could ever imagine” and 10 represented “the most intense (unpleasantness) you ever extinguish or could ever imagine experiencing.” In addition, a script derived from Price et al. (56) was read to each participant to help them distinguish between the intensity

**RESULTS**

**Subjects, side effects, and pulmonary function.** Fourteen of 22 men who signed the consent form completed the study (Fig. 1). Their descriptive characteristics are presented in Table 1. After collapsing data across CTRL and CWS conditions within each treatment period, 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 slow and forced vital capacity (FVC) by 20% (Table 2). These changes were accompanied by reductions in the forced expiratory volume in 1 s (FEV1), reductions in the forced expiratory flow rate between 25% and 75% of the FVC maneuver (FEF25–75%), and

Fig. 1. Flow diagram: enrollment, randomization, and analysis of study participants.
Comparing 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 twofold to threefold (data not shown). Compared with CTRL CWS increased the percentage contribution of leg discomfort and decreased the percentage contribution of leg discomfort to exercise cessation (Table 3). Similarly, the locus of symptom-limitation shifted away from intolerable leg discomfort to intolerable dyspnea during exercise with vs. without CWS (data not shown). 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 twofold to threefold (data not shown). Compared with placebo, nebulized fentanyl had no effect on intensity ratings of leg discomfort or on intensity and unpleasantness ratings of dyspnea during exercise with or without CWS (Tables 3 and 4, Fig. 4).

### DISCUSSION

The primary finding of our randomized, double-blind, placebo-controlled crossover study is that high-dose (250 μg) inhalation of nebulized fentanyl had no effect on exertional dyspnea (intensity or unpleasantness), exercise tolerance, or the integrated physiological response to exercise with and without external thoracic restriction in healthy (fit) young men.

Although systemic opioids are a safe and effective intervention for the management of dyspnea in cardiopulmonary disease (1, 29, 60), many healthcare providers remain skeptical of their use for fear of adverse side effects (22, 59, 79). In theory, intrapulmonary mu-opioid receptors (12, 17, 18, 34, 81) represent a promising pharmacological target in the management of dyspnea. Indeed, Simon et al. (66) and Boyden et al. (14) recently reported that sufficient evidence exists to suggest a potential benefit of nebulized fentanyl for the relief of dyspnea. Unfortunately (and in contrast to our a priori hypothesis), the results of our study do not support a role for intrapulmonary mu-opioid receptors in the neuromodulation of dyspnea, at least not in healthy (fit) younger men during exercise with or without external thoracic restriction. These findings are consistent with the results of previous randomized controlled trials reporting a lack of benefit of nebulized morphine (1.0 to 40 mg) on activity-related dyspnea or exercise tolerance in health (45) and in patients with interstitial lung disease (24) and chronic obstructive pulmonary disease (COPD) (8, 28, 38, 44). These findings also suggest that the established benefits of systemically administered opioids on dyspnea in health and disease (1, 5, 29, 60) most likely reflect a central mechanism of action.

### Methodological considerations

The question arises whether external thoracic restriction by CWS in healthy men is an

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### Table 1. Participant characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>% Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>24.9 ± 1.4</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.8 ± 0.8</td>
<td></td>
</tr>
<tr>
<td>VO₂peak, ml·kg⁻¹·min⁻¹</td>
<td>54.3 ± 2.8</td>
<td></td>
</tr>
<tr>
<td>Wmax, watts</td>
<td>241 ± 12</td>
<td></td>
</tr>
<tr>
<td>SVC, liter</td>
<td>5.24 ± 0.19</td>
<td></td>
</tr>
<tr>
<td>FVC, liter</td>
<td>5.01 ± 0.16</td>
<td></td>
</tr>
<tr>
<td>FEV₁, liter</td>
<td>4.16 ± 0.15</td>
<td></td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>83.0 ± 1.7</td>
<td></td>
</tr>
<tr>
<td>PEFR, 1s</td>
<td>9.74 ± 0.50</td>
<td></td>
</tr>
<tr>
<td>PEFR₂₅₋₇₅, 1s</td>
<td>4.60 ± 0.25</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE. CTRL, unrestricted control; CWS, chest wall strapping; SVC, slow vital capacity; PEFR, peak expiratory flow rate.

---

### Table 2. Effects of chest wall strapping, nebulized fentanyl (250 μg) and their interaction on pulmonary function test parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Fentanyl</th>
<th>Placebo</th>
<th>Fentanyl</th>
<th>Condition</th>
<th>Treatment</th>
<th>Condition*Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVC, liter</td>
<td>5.15 ± 0.15</td>
<td>5.12 ± 0.15</td>
<td>4.16 ± 0.14</td>
<td>4.16 ± 0.14</td>
<td>&lt;0.001</td>
<td>0.636</td>
<td>0.557</td>
</tr>
<tr>
<td>FVC, liter</td>
<td>5.04 ± 0.14</td>
<td>4.98 ± 0.15</td>
<td>4.10 ± 0.13</td>
<td>4.16 ± 0.16</td>
<td>&lt;0.001</td>
<td>0.982</td>
<td>0.229</td>
</tr>
<tr>
<td>FEV₁, liter</td>
<td>4.13 ± 0.15</td>
<td>4.29 ± 0.15</td>
<td>3.37 ± 0.13</td>
<td>3.40 ± 0.14</td>
<td>&lt;0.001</td>
<td>0.355</td>
<td>0.368</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>82.0 ± 2.0</td>
<td>81.9 ± 2.1</td>
<td>82.1 ± 1.8</td>
<td>82.0 ± 1.8</td>
<td>0.908</td>
<td>0.851</td>
<td>0.945</td>
</tr>
<tr>
<td>PEFR, 1s</td>
<td>9.35 ± 0.41</td>
<td>9.22 ± 0.46</td>
<td>8.37 ± 0.35</td>
<td>8.34 ± 0.41</td>
<td>&lt;0.001</td>
<td>0.735</td>
<td>0.796</td>
</tr>
<tr>
<td>PEFR₂₅₋₇₅, 1s</td>
<td>4.29 ± 0.33</td>
<td>4.31 ± 0.37</td>
<td>3.51 ± 0.25</td>
<td>3.48 ± 0.25</td>
<td>&lt;0.001</td>
<td>0.994</td>
<td>0.724</td>
</tr>
</tbody>
</table>

Values are means ± SE. CTRL, unrestricted control; CWS, chest wall strapping; SVC, slow vital capacity; PEFR, peak expiratory flow rate.
Fig. 2. Effects of chest wall strapping (CWS), nebulized fentanyl (250 μg), and their interaction on ventilatory, breathing pattern, and dynamic operating lung volume responses to constant work rate cycle exercise performed at 85% of maximal incremental work rate, equivalent to 204 ± 10 W. Data points are means ± SE at rest, standard submaximal exercise time points including isotime (6.4 ± 0.7 min) and at peak exercise. CTRLFC, unrestricted control + nebulized fentanyl; CTRLPLA, unrestricted control + nebulized placebo; CWSFC, CWS + nebulized fentanyl; CWSPLA, CWS + nebulized placebo; TLC, total lung capacity; VT, tidal volume; SVC, slow vital capacity. *P < 0.05 CWSPLA vs. CTRLPLA. †P < 0.05 CWSFC vs. CTRLFC.
Table 3. Effects of chest wall strapping and nebulized fentanyl (250 μg) and their interaction on physiological and symptom responses at the symptom-limited peak of constant work rate cycle exercise performed at 85% of maximal incremental work rate, equivalent to 204 ± 10 watts

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Fentanyl</th>
<th>Placebo</th>
<th>Fentanyl</th>
<th>Condition</th>
<th>Treatment</th>
<th>Condition*Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>V̇O₂, ml-kg⁻¹-min⁻¹</td>
<td>52.5 ± 2.6</td>
<td>52.4 ± 2.4</td>
<td>52.5 ± 2.9</td>
<td>54.4 ± 2.8</td>
<td>0.155</td>
<td>0.108</td>
<td>0.154</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>176.6 ± 2.0</td>
<td>178.0 ± 2.3</td>
<td>178.4 ± 1.7</td>
<td>178.6 ± 2.1</td>
<td>0.441</td>
<td>0.443</td>
<td>0.710</td>
</tr>
<tr>
<td>O₂ pulse, ml/O₂·beat</td>
<td>20.6 ± 1.0</td>
<td>20.4 ± 1.0</td>
<td>20.36 ± 1.2</td>
<td>21.06 ± 1.1</td>
<td>0.242</td>
<td>0.132</td>
<td>0.105</td>
</tr>
<tr>
<td>V̇E/V̇O₂</td>
<td>31.2 ± 0.8</td>
<td>32.1 ± 1.0</td>
<td>31.20 ± 0.9</td>
<td>30.8 ± 0.7</td>
<td>0.560</td>
<td>0.196</td>
<td>0.387</td>
</tr>
<tr>
<td>ṖETCO₂, mmHg</td>
<td>53.8 ± 0.9</td>
<td>36.8 ± 1.1</td>
<td>35.8 ± 1.1</td>
<td>35.8 ± 0.7</td>
<td>0.627</td>
<td>0.238</td>
<td>0.141</td>
</tr>
<tr>
<td>V̇E, l min</td>
<td>109.0 ± 4.3</td>
<td>107.9 ± 5.1</td>
<td>109.6 ± 5.6</td>
<td>111.3 ± 4.1</td>
<td>0.472</td>
<td>0.904</td>
<td>0.575</td>
</tr>
<tr>
<td>V̇̇R, liter</td>
<td>2.63 ± 0.13</td>
<td>2.71 ± 0.16</td>
<td>2.20 ± 0.10</td>
<td>2.18 ± 0.10</td>
<td>0.001</td>
<td>0.467</td>
<td>0.208</td>
</tr>
<tr>
<td>V̇̇R, %SVC</td>
<td>50.9 ± 1.8</td>
<td>52.67 ± 2.3</td>
<td>53.3 ± 2.2</td>
<td>52.7 ± 2.1</td>
<td>0.286</td>
<td>0.565</td>
<td>0.242</td>
</tr>
<tr>
<td>ḟₘₚ, breaths/min</td>
<td>42.4 ± 1.8</td>
<td>41.6 ± 2.8</td>
<td>50.3 ± 1.8</td>
<td>52.1 ± 2.2</td>
<td>0.001</td>
<td>0.739</td>
<td>0.400</td>
</tr>
<tr>
<td>IC, liter</td>
<td>3.58 ± 0.15</td>
<td>3.55 ± 0.14</td>
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<td>3.10 ± 0.15</td>
<td>0.141</td>
<td></td>
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<tr>
<td>Δ IC from rest, liter</td>
<td>0.25 ± 0.09</td>
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<td>0.27 ± 0.09</td>
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</tbody>
</table>

Values are means ± SE. V̇O₂/V̇ETCO₂, ventilatory equivalent for carbon dioxide; ṖETCO₂, end-tidal partial pressure of carbon dioxide; V̇E, minute ventilation; V̇̇R, tidal volume; SVC, slow vital capacity; ḟₘₚ, breathing frequency; IC, inspiratory capacity; Δ, change; IRV, inspiratory reserve volume; 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. *Measured using the Borg 0–10 scale.

Table 4. Effects of chest wall strapping and nebulized fentanyl (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% of maximal incremental work rate, equivalent to 204 ± 10 watts

<table>
<thead>
<tr>
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</tbody>
</table>

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appropriate model for studying the potential therapeutic benefits of nebulized opioids on exertional dyspnea in adults with RLDs. In our study, CWS sufficient to decrease vital capacity by \(\frac{1}{10} \times 20\%\) in men successfully mimicked the consequences of a mild RLD on detailed physiological and perceptual responses at rest and during exercise (23, 42, 50, 52, 73) without the potentially confounding influences of psycho-physiological comorbidities, deconditioning, hypoxemia, concomitant medication use, etc., which may themselves contribute to dyspnea and mask the potential benefits of nebulized fentanyl in persons with RLDs. In this regard, and in keeping with the results of earlier studies (25, 46, 51), CWS was associated with reductions in FEV1, FEF25–75%, IC, and inspiratory reserve volume at rest; relative preservation of the FEV1/FVC ratio; reduced exercise endurance time; increased dynamic mechanical ventilatory constraints, tachypnea, and increased neural respiratory drive during exercise; a shift in the locus of symptom-limitation from leg discomfort to dyspnea; and clinically meaningful increases in the intensity and unpleasantness of exertional dyspnea, which was described as a heightened sense of unsatisfied inspiration.

Certain limitations of using the CWS-model warrant consideration of course. External thoracic restriction in health only mimics diseases/disorders of the chest wall, such as kyphoscoliosis, pectus excavatum, pectus carinatum, ankylosing spondylitis, flail chest, and fibrothorax. As such, CWS in health does not accurately reproduce the intrinsic mechanical loads or the long-term sensory effects of many RLDs (e.g., interstitial lung disease, interstitial pulmonary fibrosis) nor does it replicate the inflammatory component of chronic pulmonary diseases commonly associated with activity-related dyspnea (e.g., COPD). Furthermore, acute CWS in health does not likely reflect the long-term adaptations to skeletal muscle architecture or sensory receptors that may accompany pathologies of the chest wall.

Clinical and experimental observations suggest that the analgesic potency of opioids is increased in the presence of tissue inflammation and injury (80). Indeed, evidence suggests that tissue inflammation and damage upregulate the synthesis, expression, sensitivity, and axonal transport of mu-opioid receptors toward the peripheral sensory nerve endings, including those in the airways (57, 69, 80). Inflammation also disrupts...
the perineural sheath thus increasing, at least in theory, the accessibility of inhaled mu-opioid receptor agonists to their corresponding receptor subtype (3, 69). 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 (6, 69). Indeed, in vitro studies have shown an inhibitory effect of mu-opioids on factors known to contribute to the pathophysiology and symptoms (e.g., dyspnea) of chronic inflammatory airway disease, including cholinergic neurotransmission and contraction of airway smooth muscle (7, 11, 55), neurogenic mucus hypersecretion (61), goblet cell secretion (35), and plasma extravasation (10, 65). It is thus possible that the lack of benefit of nebulized fentanyl on exertional dyspnea in our study may be explained at least in part by inclusion of healthy younger men with no known or suspected history of chronic inflammatory airway disease. In other words, intrapulmonary mu-opioid receptors may not have been particularly sensitive, abundant, or accessible to the analgesic effect(s) of nebulized fentanyl in our participants.

Our study was designed so that any change in dyspnea would most likely reflect a pulmonary vs. central mechanism of action of nebulized fentanyl. First, Worsley et al. (78) reported that serum fentanyl levels following inhalation of 300 µg of nebulized fentanyl reached a plateau at 0.1 ng/ml after 15 min, indicating very low systemic bioavailability. In our study, exercise tests were initiated ~45 min after inhalation of a slightly lower dose (250 µg) of nebulized fentanyl when systemic bioavailability was presumably negligible. Second, we optimized delivery of fentanyl to the airways and lungs by studying healthy men without airway inflammation/obstruction/secretions (48); administering a relatively high nebulized dose of fentanyl through a mouthpiece (vs. open facemask) during deep and deliberate tidal inspirations (48); and using a nebulizer that produced particles with a mass median diameter (~5 µm) capable of traversing the small airways and anatomical dimensions of the alveoli (49, 75). Nevertheless, it is very difficult to confirm that some or all of the inhaled nebulized fentanyl reached the intrapulmonary mu-opioid receptors.

Exercise tests were initiated ~45 min postnebulization, thus the lack of effect of nebulized fentanyl on measured parameters may reflect diminution of its analgesic potency at the level of the intrapulmonary mu-opioid receptors. However, studies that initiated exercise testing ≤30 min after nebulization of morphine also reported no benefit on activity-related dyspnea or exercise performance in health (45), interstitial lung disease (24), and COPD (28, 38, 44). Furthermore, and although information was not available for pulmonary administration, the product monograph for the fentanyl used in our study 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, 60–120 min, and 120–300 min, respectively. Nevertheless, termination of the action of fentanyl in the lung may be more rapid than in the peripheral circulatory system due to the high specific blood flow characteristic of the lung. As such, we cannot rule out the possibility that diminution of the analgesic potency of fentanyl at the level of the intrapulmonary mu-opioid receptors was at least partly responsible for our negative results.

Although we estimated a priori that 28 participants were needed to detect a ±1 Borg 0–10 scale unit difference in dyspnea intensity ratings at isotime among the four conditions, a blinded efficacy analysis of the first 14 men completing our study provided no clear evidence of a potentially significant or meaningful treatment effect or treatment × condition interaction on our primary outcome variable. A decision was made on ethical grounds to cease our trial after testing 50% of our a priori minimum samples size. Thus we cannot preclude the possibility that a type II statistical error was at least partly responsible for our negative results.

In summary, our findings do not support a role for intrapulmonary mu-opioids in modulating the intensity or unpleasantness dimensions of dyspnea during constant work rate cycle exercise performed at 85% of maximal incremental work rate, equivalent to 204 ± 10 W. Data points are means ± SE at rest, standard submaximal exercise time points including isotime (6.4 ± 0.7 min), and at peak exercise. *P < 0.05 CWSPLA vs. CTRLPLA. †P < 0.05 CWSFC vs. CTRLFC.

Fig. 4. Effects of CWS, nebulized fentanyl (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 W. Data points are means ± SE at rest, standard submaximal exercise time points including isotime (6.4 ± 0.7 min), and at peak exercise. *P < 0.05 CWSPLA vs. CTRLPLA. †P < 0.05 CWSFC vs. CTRLFC.
of exertional symptoms in mild, restrictive pulmonary disorders, specifically those arising from abnormalities of the chest wall and not affiliated with airway inflammation.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

H.G.K., J.B., and D.J. conception and design of research; H.G.K. and D.J. performed experiments; H.G.K. and D.J. analyzed data; H.G.K., J.B., and D.J. interpreted results of experiments; H.G.K. and D.J. prepared figures; H.G.K. and D.J. drafted manuscript; H.G.K., J.B., and D.J. edited and revised manuscript; H.G.K., J.B., and D.J. approved final version of manuscript.

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