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Endogenous Opioids Modify Dyspnea during Treadmill Exercise in Patients with COPD

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Short title: Endogenous opioids modify exertional dyspnea

Abstract

Exogenous opioid drugs, such as morphine, relieve breathlessness. Our hypothesis is that endogenous opioids, released during the stress of exercise, modify dyspnea in patients with chronic obstructive pulmonary disease.

After familiarization, patients performed an incremental treadmill exercise test followed by constant work on the treadmill for 10 minutes. At subsequent visits (2 to 3 days apart): patients received 2 puffs of albuterol; had a catheter placed in an arm vein for removal of blood to measure beta-endorphin immunoreactivity; received normal saline or 10 mg of naloxone intravenously in randomized order; and then performed high intensity constant work rate exercise on treadmill.

Age of the seventeen patients (8 females/9 males) was 63 ± 7 years, and post-bronchodilator FEV_1 was 50 ± 17 % predicted. In both conditions beta-endorphin levels increased three-fold from rest to end-exercise. The regression slope of breathlessness as a function of oxygen consumption (primary outcome), mean ratings of breathlessness throughout exercise, and peak ratings of breathlessness were significantly higher with naloxone than normal saline. There were no differences in physiological responses throughout exercise between conditions.

We conclude that endogenous opioids modify dyspnea during treadmill exercise in patients with chronic obstructive pulmonary disease by apparent alteration of central perception.

Key words: treadmill exercise; continuous ratings of breathlessness; naloxone; beta-endorphin immunoreactivity; chronic obstructive pulmonary disease

Word count: 200

INTRODUCTION

Dyspnea, or breathlessness, is the most frequent symptom of patients with chronic obstructive pulmonary disease (COPD). Based on a neurophysiological model, breathlessness occurs when sensory receptors involved with respiration are activated and send an afferent impulse to the central nervous system (CNS). After integration and processing of this signal, the CNS directs an efferent impulse toward the muscles of respiration . Any alteration of the sensory receptors, the CNS, and/or the respiratory muscles could lead to a dissociation or "mismatch" between outgoing motor signals from the CNS and the mechanical response of the respiratory system, and thereby contribute to breathlessness [1].

Exogenous opioid drugs, such as dihydrocodeine and morphine, reduce the intensity of exertional breathlessness in patients with COPD [2, 3]. In1985 Santiago and Edelman [4] postulated that endogenous opioids might be elaborated as a protective mechanism to relieve breathing difficulty when respiratory distress occurred. Naloxone, an opioid antagonist, has been used in numerous studies to examine the putative role of endorphins on breathing. Using hypoxia, hypercapnia, inspiratory resistance breathing, and exercise on the cycle ergometer as respiratory stimuli, investigators have been unable to demonstrate an effect of endorphins on respiration and/or breathlessness in patients with COPD [5-7]. In one study Santiago and colleagues [8] reported that naloxone restored the ventilatory responses to an added inspiratory flow-resistive load in 7 of the 14 patients with COPD in whom "load compensation" was absent.

In the present study we examined the hypothesis that endogenous opioids modify the severity of exertional breathlessness in patients with symptomatic COPD. A secondary hypothesis was that patients would exercise longer with normal saline

compared with blockade of the endogenous opioid system. The study design incorporated different methodology than used previously to examine these hypotheses. Constant work rate on the treadmill was used as the exercise stimulus rather than cycle ergometry because walking is a relevant daily activity and provokes breathlessness to a greater extent than does cycling in patients with COPD [9, 10]. The speed and incline of treadmill exercise were individualized so that each patient walked for at least 10 minutes in an attempt to provide an adequate respiratory challenge. Patients reported the actual course of breathlessness throughout exercise using a continuous rating system rather than providing ratings "on cue" at discrete time periods [11]. Preliminary results of this investigation have been presented in abstract form [12].

MATERIALS AND METHODS

Subjects

Patients with a diagnosis of COPD were recruited from the out-patient clinics at our institution. The protocol was approved by the Committee for the Protection of Human Subjects at Dartmouth College. All patients provided informed written consent. Inclusion criteria were: $\geq$ 50 years of age; diagnosis of chronic obstructive pulmonary disease [13]; self-reported rating of breathlessness on the baseline dyspnea index (BDI) of $\leq$ 8 [14]; $\geq$ 10 pack-year history of cigarette smoking; ability to exercise on the treadmill; and clinically stable.

As there is limited information available about a relevant difference in the regression slope between breathlessness and VO_2 (the primary outcome), we used a rating of breathlessness of ± 1 with a SD of 1 at a standardized work rate as an estimate to calculate the sample size [15]. A sample size of 16 was used to provide the power (80%) to detect a significant difference in standardized breathlessness ratings, $\alpha = 0.05$

Study Design

The main objective was to compare the effects of intravenous administration of normal saline and naloxone on ratings of dyspnea during constant work rate treadmill exercise. The study design was randomized and double-blind. After familiarization with equipment and procedures, each patient performed spirometry (Collins model CPL; Louisville, CO) and an incremental treadmill (Full Vision Inc.; Newton, KS) exercise test using a modified Balke protocol [16]. After a one hour rest, each patient walked on the treadmill to establish the speed and incline for the constant work rate exercise used at subsequent testing. The treadmill speed was the same as obtained for each patient during the incremental exercise test, while the incline of the treadmill was adjusted so that the patient could exercise for 10 minutes at a high intensity of breathlessness [11].

There were two intervention study visits, 2 – 3 days apart. Patients were instructed not to take any inhaled medications for 12 hours and to avoid caffeine for four hours prior to each visit. Testing was performed at the same time of day for each subject. Patients performed spirometry before and 30 minutes after inhaling 2 puffs of albuterol (180 μg). Predicted values for spirometry were taken from Crapo et al. [17]. An 18 gauge catheter was inserted into an arm vein for measurement of beta-endorphin immunoreactivity. The subject sat in a chair while breathing quietly through the mouth piece for five minutes. After 10 ml of venous blood was removed, normal saline (25 ml) or naloxone (10 mg in 25 ml total volume) was administered intravenously in random order. Patients continued to breathe quietly through the mouth piece for five minutes, and then performed a symptom-limited constant work exercise test according to recommended guidelines [16]. Each patient was strongly encouraged to exercise for "as long as possible" with a target of 10 minutes as a minimum. The exercise tests were

terminated when the patient indicated that he/she could no longer continue. At the end of each exercise test the patient was asked, "Why did you stop exercise: breathlessness, leg discomfort, or both?"

Expired gas was analyzed for minute ventilation (V_E), oxygen consumption (VO_2), and carbon dioxide production (VCO_2) at rest and throughout exercise using a metabolic measurement system (MedGraphics Cardiorespiratory Diagnostic Systems, St. Paul, MN). The system was calibrated before each test. Oxygen saturation was recorded using a pulse oxymeter (Nellcor Inc., Hayward, CA).

The patient rated breathlessness and leg discomfort throughout exercise using a continuous method that consisted of a computer, a monitor, and a mouse as previously described [11]. At each visit, the patient read the following written instructions.

> "This is a scale for rating breathlessness and leg discomfort. The number 0 represents no breathlessness and no leg discomfort. The number 10 represents the strongest or greatest breathlessness or leg discomfort that you have ever experienced. You should adjust the length of the blue bar to represent your perceived level of breathlessness by pressing the left button on the mouse. You should adjust the length of the red bar to represent your perceived level of leg discomfort by pressing the right button on the mouse. Use the written descriptions to the right of the numbers to help guide your selection. You should increase the length of each bar whenever you experience a change in breathlessness or leg discomfort."

Beta-endorphin immunoreactivity. Ten milliliters of venous blood were removed from the catheter using a chilled syringe and then immediately emptied into chilled tubes containing EDTA anticoagulant while the patient was seated in a chair on three occasions (after five minutes of rest, within one minute of completion of exercise, and 30 minutes after completion of exercise). With these specimens plasma beta (β)-endorphin immunoreactivity was measured using a Beckman Gamma 5500 System with data processor as previously described [18].

Statistical Analysis

The primary outcome was the regression slope between breathlessness and VO_2 [15, 19, 20]. Secondary outcomes were peak and mean ratings of breathlessness throughout exercise, exercise duration, the regression slope between breathlessness and V_E, and plasma beta (β)-endorphin immunoreactivity.

Paired t-tests were used to compare outcomes. Pearson correlation coefficient was used to examine differences in mean ratings of breathlessness and differences in exercise time between the two conditions**.** All data are reported as mean ± SD. A *p* value $\leq$ 0.05 (two-tailed test) was considered statistically significant.

RESULTS

Seventeen patients (8 females/9 males) participated in this study (Figure 1). Age was 63 ± 7 yrs; height was 168 ± 8 cm; and weight was 74 ± 14 kg. As a group, the patients reported moderate breathlessness related to activities of daily living on the self-administered computerized BDI (5.7 ± 1.4). Respiratory medications were albuterol MDI (n=17), inhaled long-acting beta-agonist (n=11), inhaled short or long-acting anticholinergic medication (n=14), inhaled corticosteroids (n=8), and oral theophylline (n=3).

The results of lung function measurements are given in Table 1.

Table 1. Results of lung function

	Naloxone	Normal saline
FVC		
(liters)	3.05 ± 0.70	3.01 ± 0.62
% predicted	84 ± 14	83 ± 12
FEV_1		

Baseline (liters)	1.15 ± 0.36	1.14 ± 0.35
% predicted	45 ± 15	45 ± 14
Post-BD (liters)	1.27 ± 0.39	1.24 ± 0.34
% predicted	50 ± 17	49 ± 15
Post-BD FEV_1/FVC (%)	39 ± 12	39 ± 11

FVC = forced vital capacity

FEV_1 = forced expiratory volume in one second

Post-BD = post-bronchodilator

The number of patients in the different stages of COPD based on post-bronchodilator FEV_1 % predicted were [13]: II – eight; III - eight; IV – one. There were no significant differences for pre- or post-bronchodilator values for lung function between the two visits.

Resting values for heart rate and for respiratory variables were similar between naloxone and normal saline. Results from constant work treadmill exercise (speed: 1.9 ± 0.8 mph; grade: 3.8 ± 2.1 %) are presented in Table 2.

Table 2. Results of constant work treadmill exercise

	Naloxone	Normal saline	p value (95% CI)
Peak values			
VO_2 (ml/kg/min)	15.5 ± 5.2	15.3 ± 5.4	0.22

			(-0.17, 0.71)
V_E (l/min)	36.5 ± 12.4	35.7 ± 12.5	0.18
			(-0.42, 2.08)
VCO_2 (l/min)	1.0 ± 0.3	1.0 ± 0.3	0.60
			(-0.03, 0.06)
f_R (breaths/min)	34 ± 9	34 ± 10	0.76
			(- 1.83, 1.34)
HR (beats/min)	129 ± 18	130 ± 16	0.19
			(-1.55, 4.12)
SaO_2 (%)	92.5 ± 3.3	91.8 ± 4.2	0.07
			(- 1.64, 0.26)
Breathlessness	8.7 ± 2.3	8.0 ± 2.3	0.05
			(- 0.00, 1.42)
Leg discomfort	5.9 ± 3.2	5.5 ± 3.3	0.27
			(- 0.37, 1.23)
Endurance time	12:20 ± 4:05	14:01 ± 4:05	0.058
(min:sec)			(- 101, 177)
Reason for stopping exercise			
Breathlessness	15	15	
Leg discomfort	2	2	
<u>Regression slopes</u>			
Breathlessness – VO_2	3.34 ± 1.93	2.51 ± 2.10	0.02
			(0.13, 1.53)

Breathlessness - V_E	0.87 ± 1.00	0.76 ± 0.88	0.32 (- 0.47, 0.71)
Leg discomfort – VO_2	2.23 ± 1.66	1.86 ± 1.69	0.38 (- 0.49, 1.22)

CI = confidence interval; VO_2 = oxygen consumption; V_E = minute ventilation; VCO_2 = carbon dioxide production

f_R = frequency of respiration; HR = heart rate; SaO_2 = arterial oxygen saturation

There were no differences in VO_2 or V_E values when compared every 2 minutes throughout constant work rate exercise under the two conditions (Figure 2). Peak physiologic variables were similar between naloxone and normal saline. The highest VO_2 values represented 92% of peak VO_2 (16.7 ± 5.4 ml/kg/min) obtained during the incremental treadmill exercise test. The mean ratio of peak V_E to the calculated maximal voluntary ventilation (FEV_1 x 40) was 82%. Individual values for the slope of breathlessness and VO_2 are shown in Figure 3. Paired-t testing showed that the regression slope of breathlessness and VO_2 was significantly higher with naloxone than with normal saline ($p = 0.02$). This difference remained statistically significant after elimination of one patient (stage II disease) who exhibited the greatest difference between naloxone and normal saline. Peak ratings of breathlessness were significantly higher with naloxone compared with normal saline ($p = 0.05$). Individual differences in mean ratings of breathlessness throughout exercise between naloxone and normal saline were significant ($p = 0.04$) (Figure 4). There was a trend showing a greater exercise time

with normal saline compared with naloxone (Δ = 1min, 41 sec; p = 0.058). There was no difference in the slope of breathlessness and V_E between treatments. The correlation between differences in mean ratings of breathlessness and differences in exercise time was – 0.07.

Table 3 shows the levels of β-endorphin immunoreactivity at the three time periods.

Table 3. Levels of β-endorphin immunoreactivity

β-endorphin immunoreactivity	Naloxone	Normal saline	p value (95% CI)
Baseline	6.3 ± 2.0	6.0 ± 1.8	0.45 (- 0.46, 0.99)
End exercise	19.8 ± 4.7	19.3 ± 5.5	0.72 (- 2.57, 3.64)
30 minutes post-exercise	8.7 ± 2.6	7.8 ± 1.7	0.15 (- 0.37, 2.22)

CI = confidence interval; values for β-endorphin immunoreactivity are in pg/ml

Patients exhibited an increase in β-endorphin immunoreactivity from rest to peak exercise ($p < 0.001$), and a decrease post-exercise compared with peak values ($p < 0.001$). There were no significant differences in β-endorphin immunoreactivity at corresponding time periods between naloxone and normal saline.

DISCUSSION

The major findings of this study are: 1) patients report greater breathlessness during exercise with naloxone compared with normal saline; 2) plasma β-endorphin levels increased similarly during exercise with naloxone and normal saline; 3) there is a non-significant trend for patients to exercise longer with normal saline compared with naloxone.

Endogenous opioids are widely distributed in areas of the CNS and act as neurotransmitters of a complex inhibitory system [4]. Of the five groups of naturally occurring opioid peptides, β-endorphins contribute to pain perception, and have been widely studied in regard to respiration [4, 21]. Both circulating β-endorphins, which are produced by the pituitary gland, and levels found in the cerebrospinal fluid (CSF), which are elaborated in the brain, increase in response to strenuous exercise in healthy individuals [21]. To our knowledge, our study is the first to report the response of circulating β-endorphins to exercise in patients with COPD. When injected into the vicinity of the medulla in animals, β-endorphins depress breathing primarily by reducing tidal volume [22]. This response is similar to the effect of oral morphine in humans [23].

Naloxone, an opioid antagonist which readily crosses the blood-brain barrier, has been used to uncover the putative effects of endogenous opioids. In our study, patients with COPD reported higher ratings of breathlessness throughout treadmill exercise after administration of naloxone compared with normal saline. The variability of individual responses is illustrated in Figures 3 and 4. We prospectively selected the regression slope between breathlessness and VO_2 as the primary outcome measure for several reasons. First, this parameter represents a continuum of the relationship between overall metabolic activity and the perception of breathlessness. It provides more comprehensive information compared with a single rating at exercise iso-time or at end-exercise. Second, the regression slope between breathlessness and VO_2 during exercise is an established metric that has been used by investigators to discriminate

between different populations and to examine treatment effects in patients with COPD [11, 15, 20]. Third, the regression slope between continuous ratings of breathlessness and VO_2 has demonstrated responsiveness [19]. The actual value for the regression slope between breathlessness and VO_2 with normal saline, used as a control condition in this study, approximated the value that we obtained previously when patients with COPD performed incremental treadmill exercise [24].

The higher ratings of breathlessness at peak exercise (Table 2) and mean ratings throughout exercise (Figure 4) after administration of naloxone support the results of the primary outcome. The display of individual differences in mean ratings of breathlessness is a novel approach that reflects the collective experience of breathlessness reported by patients throughout exercise. These data complement the usual method of calculating the regression slope between breathlessness and VO_2. We are unable to display plots of breathlessness against time or VO_2 because the continuous reporting method makes it difficult to anchor symptom ratings to a specific physiological stimulus.

To our knowledge, this study is the first to demonstrate that endorphins modulate exertional breathlessness. Although there has been wide interest in the role of endorphins in breathing for some time, previous investigators failed to show any direct effect. For example, Kirsch and colleagues [5] reported no differences in perceptual responses between naloxone and normal saline in six patients with COPD who performed incremental cycle ergometry and rated breathlessness each minute of the test. In a preliminary report, Bertley and associates [6] found that 5 of 12 patients with COPD were “responders” based on their increased ratings of breathlessness after receiving naloxone compared with normal saline.

Although our study examined the same hypothesis as proposed by these investigators, we used different methodology. Treadmill walking was used to provoke breathlessness rather than

cycling, based on recent studies showing that breathlessness is more limiting during walking, whereas leg complaints are more common with cycling [9, 10]. Our patients exercised at a high intensity (92% of peakVO_2 on the treadmill) during constant work exercise in an attempt to provide an adequate respiratory stress or challenge, whereas incremental cycle ergometry of shorter duration (~ 5 – 6 minutes) was the stimulus in previous studies [5, 6]. Our patients reported symptoms continuously throughout exercise; this approach provides several advantages compared with the discrete method [11, 19].

Previous laboratory investigations support the role of endorphins in modifying the perception of breathlessness with respiratory challenges. For example, Bellofiore and colleagues [25] found that six asymptomatic patients with asthma reported higher breathlessness ratings after naloxone compared with normal saline when bronchoconstricted by inhaling methacholine. Akiyama and colleagues [26] reported that 12 healthy young adults had an increase in breathlessness while breathing carbon dioxide after naloxone administration.

As a secondary hypothesis, we proposed that patients would exercise longer with normal saline compared with blockade of the endogenous opioid system. Although 11 of the 17 patients with COPD exercised longer on the treadmill with normal saline than with naloxone, the difference did not achieve statistical significance ($p = 0.058$). However, the observed difference in exercise duration (mean Δ = 1 min and 41 sec) between conditions was comparable to improvements in exercise time observed with bronchodilator medications (compared with placebo) in patients with COPD performing constant work cycle ergometry [27, 28]. Our data suggest an effect of naloxone on treadmill exercise endurance. A larger number of patients would be required to investigate this hypothesis.

Possible mechanisms for the action of opioids in modifying breathlessness are a reduction in ventilation, a reduction in oxygen consumption, and an alteration in the central perception of breathlessness. Figure 2 demonstrates clearly that VO_2 and V_E values were identical throughout exercise between naloxone and normal saline conditions. In addition, the relationship between V_E and metabolic parameters (VO_2 and VCO_2) during exercise was unaltered with naloxone compared with normal saline. These results are consistent with other findings described at rest and/or at peak exercise in patients with COPD [5, 29]. Previous studies also showed that naloxone had no effect on the ventilatory response to hypercapnia in patients with COPD, and in healthy subjects upon completion of running a marathon [18, 29]. As neither ventilatory responses nor VO_2 was affected by administration of naloxone, it appears that endogenous opioids alter the central perception of breathlessness. This mechanism is consistent with the observed benefit of using exogenous opioids, such as narcotic medications, for relieving dyspnea in patients with advanced or end-stage disease.

One limitation of this investigation is the modest number of patients that we studied. As there was variability of individual responses, a larger number of participants may have provided sufficient power to demonstrate a significant difference in exercise endurance between naloxone and normal saline. Although we attempted to recruit additional patients for this study, several individuals declined participation because of their concern about placement of an intravenous catheter and of possible adverse effects of the intravenous naloxone (Figure 1). Another possible limitation is the dose of naloxone used in our study. The 10 mg dose was selected based on previous investigations [7, 18]. Based on the body weight of our patient group (74 ± 14 kg), the 10 mg dose generally exceeds the dose of 0.1 mg/kg used by some other investigators [6,

25, 30]. It is possible that a dose of naloxone > 10 mg may have contributed to a greater effect in some patients.

These results expand our understanding how natural biological responses can modify breathlessness under the stress of physical exercise. These findings are consistent with the effect of endogenous opioids in relieving pain. Animal studies show that the pain threshold increases after exercise, and this effect can be partially altered by administration of naloxone [21]. In a study of humans, the threshold for dental pain was elevated by 30% after exercise compared to a control condition [31]. Thoren and colleagues [21] proposed that prolonged rhythmic exercise can activate central opioid systems by triggering discharge from mechanosensitive afferent nerve fibers arising from contracting muscles. Whether the relief of breathlessness experienced by patients with COPD who perform exercise training as part of pulmonary rehabilitation is mediated, in part, by the endogenous opioid system requires investigation.

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Clinical trial registered with www.clinicaltrials.gov (NCT00458419).

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Figure Legend

Figure 1. Diagram of enrollment, allocation, follow up, and analysis of patients.

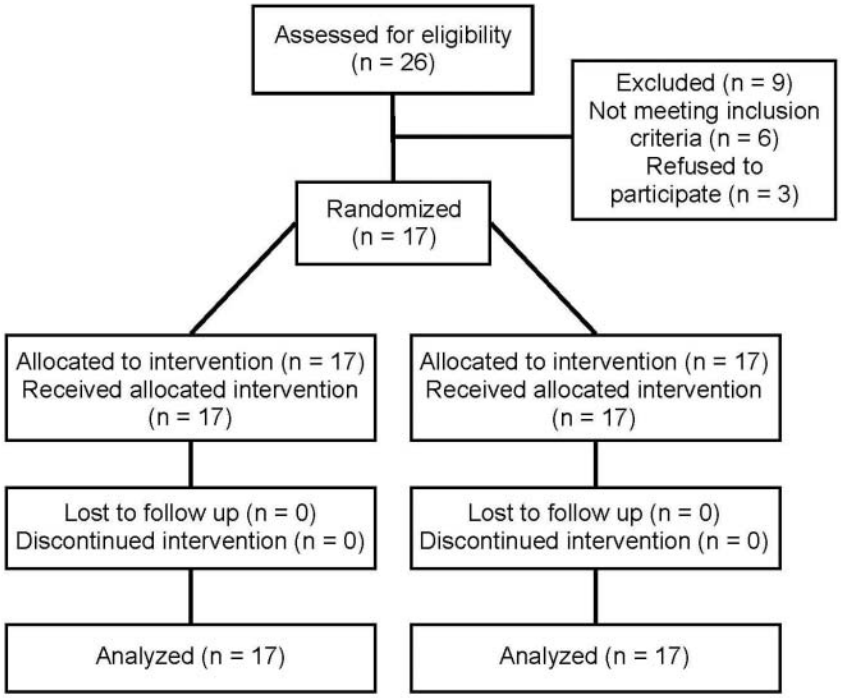
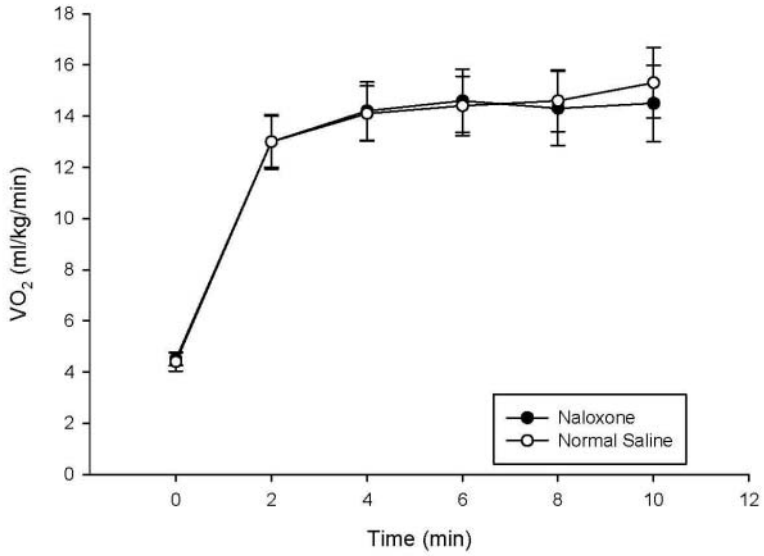


Figure 2. Mean and standard error values for oxygen consumption (VO_2) (Figure 2A) and

minute ventilation (V_E) (Figure 2B) every two minutes during the first 10 minutes of constant work rate exercise on the treadmill. There were no differences for VO_2 and V_E at any time periods between naloxone and normal saline. For time periods 0 – 6 minutes, n = 17 for each group. At 8 and 10 minutes, n = 14 for the naloxone group and n = 17 for the normal saline group.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2
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VO_2 (ml/kg/min)
0
2
4
6
8
10
12
Time (min)
Naloxone
Normal Saline

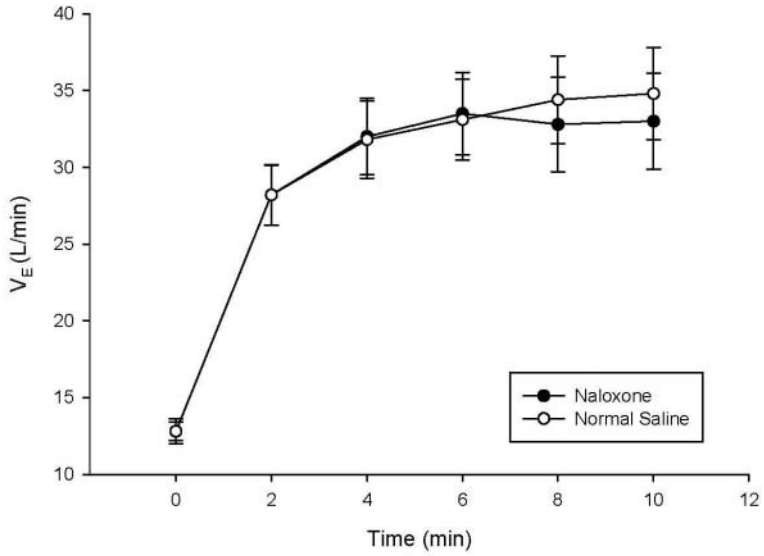

Figure 3. Individual values for the regression slope of breathlessness and oxygen consumption (VO_2) with administration of naloxone and normal saline. The dashed line

is the line of identity. Paired t-tests showed a significant difference between naloxone and normal saline ($p = 0.02$). Individual patients are identified by their stage of disease severity using different symbols based on percent predicted values for forced expiratory volume in one second [13].

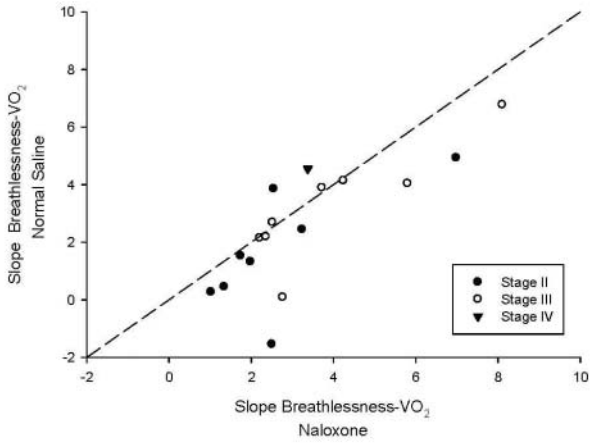

Figure 4. Individual differences in mean ratings of breathlessness throughout exercise between naloxone and normal saline. Paired t-tests showed a significant difference

between naloxone and normal saline (p = 0.04). Patients provided similar numbers of ratings of breathlessness throughout exercise with naloxone (20.9 ± 7.2) and with normal saline (20.1 ± 7.5) (p = 0.47).