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Energy efficient physiologic coupling of gait and respiration is altered in chronic obstructive pulmonary disease

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Abstract

Aims: Coupling between walking and breathing in humans is well established. In healthy systems, the ability to couple and uncouple leads to energy economization. It is unknown if physiologic efficiency is susceptible to alteration particularly in individuals with airflow obstruction. The aim of this research was to determine if coupling was compromised in a disease characterized by abnormal airflow and dyspnea, and if this was associated with reduced energy efficiency.

Methods: As a model of airflow obstruction, 17 chronic obstructive pulmonary disease (COPD) patients and 23 control subjects were included and walked on a treadmill for six-minutes at three speeds (preferred speed and ±20% preferred speed) while energy expenditure, breathing, and walking were recorded. Rating of perceived exertion was recorded at the end of each walking trial. The most commonly used frequency ratio (i.e. strides:breath) and cross recurrence quantification analysis were used to quantify coupling. Linear regression models were used to determine associations.

Results: Less complex frequency ratios, simpler ratios, (i.e. 1:1 and 3:2) accompanied with stronger coupling were moderately associated with increased energy expenditure in COPD subjects. This was found for all three speeds.

Conclusion: The novel finding was that increased energy expenditure was associated with stronger and less complex coupling. Increased effort is needed when utilizing a frequency ratio of 1:1 or 3:2. The more stable the coupling, the more effort it takes to walk. In contrast to the

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CONFLICT OF INTEREST
Dr. Stephen Rennard is employed by AstraZeneca, Cambridge, UK and also retains Professorship and a part-time appointment at the University of Nebraska Medical Center, Omaha, NE, USA. Dr. Rennard reports personal fees from the Japanese Respiratory Society. No other author reports a conflict of interest.

complex energy efficient coupling of controls, those with airflow obstruction manifested simpler and stronger coupling associated with reduced energy efficiency.

Keywords

cost of transport; entrainment; locomotor respiratory coupling; recurrence quantification analysis; VO2

INTRODUCTION

Extensive research demonstrates the presence of entrainment of movement and respiration in normal humans.[1–6] It is well established that breathing and walking patterns strongly influence each other, a process called locomotor respiratory coupling.[6–10] There have been several pathways proposed that may mediate this coupling.[8,11–16] A relationship between coupling of breathing and movement and energy expenditure exists.[17,18] When rhythms are optimally coupled, energy expenditure is economized.[10,19,20] Creating a stronger or more stable coupling between the two systems has led to a decrease, increase, or little impact on energy expenditure.[6,8–10,18–24] Further, the variability in locomotor respiratory coupling frequency is important, as this may be a strategy to find a coupling that optimizes energy expenditure.[7,18,20] What is unknown is whether physiological efficiency is susceptible to alteration with disease states. In particular, how does airway obstruction affect the association between energy expenditure and locomotor respiratory coupling.

Chronic obstructive pulmonary disease (COPD) is defined in terms of fixed airflow limitation and is characterized by the frequent association of disease outside the lung.[25,26] Compared to healthy controls, patients with COPD have a more regular breathing pattern and the regularity proportionally increases with airway obstruction.[27] In addition, patients with COPD demonstrate altered variability in their walking pattern as compared to their healthy counterparts.[28] Previous research demonstrates that patients with COPD display an unvarying locomotor respiratory coupling pattern (i.e., one stride to one breath) under various walking speeds.[29–31] Further, patients with COPD have increased energy expenditure.[32–35] Patients with COPD present with abnormal breathing, hypoxemia, and/or other metabolic impairments likely contribute to this increased energy expenditure. As has been shown,[29–31] patients with COPD have strong and simple coupling, suggesting limited options to exploit more efficient strategies than controls, which could synergize with these other mechanisms, thereby increasing energy cost. Therefore, it is plausible that abnormal coupling between breathing and walking in patients with COPD may contribute to increased energy expenditure.

The current study was designed to determine if efficient locomotor respiratory coupling was compromised in COPD, a disease characterized by abnormal airflow and dyspnea, and further, if coupling was associated with reduced energy efficiency compared to aged-matched, healthy controls. It was hypothesized that patients with COPD would demonstrate strong but simple coupling between breathing and walking and that it would be associated with increased energy expenditure as compared to their healthy counterparts. This hypothesis was tested under three different walking speeds to determine the effect of task demands on this relationship. Defining an alteration in this linking will help illuminate altered physiologic efficiency associated with airflow obstruction.

RESULTS

Descriptive results

Preferred walking speed was slower in patients with COPD compared to controls ($p=0.001$; Figure 1, top). Rating of perceived exertion was significantly higher in patients with COPD compared to controls across all speeds ($F_{1,38}=11.9$; $p=0.001$) and significantly increased with speed across both groups ($F_{2,76}=29.1$; $p<0.001$) (Figure 1, middle). Cost of transport was significantly increased in patients with COPD during the preferred walking speed ($p = 0.023$; Figure 1, bottom). Patients with COPD used less complex frequency ratios (e.g., 1:1) more often compared to controls (Figure 2).

Cross recurrence quantification analysis (cRQA) Percent Determinism was significantly more periodic in patients with COPD compared to controls across all speeds ($F_{1,38}=5.8$; $p=0.02$) and significantly decreased with speed across both groups ($F_{2,76}=4.8$; $p=0.01$) (Figure 3, top left). cRQA Maximum Line was significantly longer in patients with COPD compared to controls across all speeds ($F_{1,38}=8.2$; $p=0.007$). cRQA Mean Line was significantly longer in patients with COPD compared to controls across all speeds ($F_{1,38}=5.0$; $p=0.03$) and significantly decreased with speed across both groups ($F_{2,76}=4.7$; $p=0.01$) (Figure 3, bottom left). cRQA Entropy was significantly less regular in patients with COPD compared to controls across all speeds ($F_{1,38}=4.2$; $p=0.046$) and significantly more regular as speed increased across both groups ($F_{2,76}=6.0$; $p=0.004$) (Figure 3, bottom right).

Spearman Correlations

At preferred walking speed and both groups combined, a more complex frequency ratio (i.e., 4:1) was moderately and inversely associated with perceived exertion ($\rho = -0.38$, $p = 0.015$ Figure 4, top left) and cost of transport ($\rho = -0.40$, $p = 0.011$; Figure 4, middle left). A longer cRQA Maximum Line was moderately associated with increased cost of transport ($\rho = 0.47$, $p = 0.002$ Figure 4, bottom left).

When walking at −20% of preferred speed, a more complex frequency ratio was moderately and inversely associated with both perceived exertion ($\rho = -0.48$, $p = 0.002$ Figure 4, top right) and cost of transport ($\rho = -0.38$, $p = 0.017$ Figure 4, middle right). Whereas, at +20% of preferred walking speed, a longer cRQA Maximum Line was moderately associated with an increased cost of transport ($\rho = 0.31$, $p = 0.049$ Figure 4, bottom right).

Regression Analysis

For preferred walking speeds, separate models assessing differences between patients with COPD and healthy controls were generated for each coupling outcome variable, while controlling for either rating of perceived exertion or cost of transport. For models which adjusted for rating of perceived exertion, patients with COPD had significantly increased cRQA Percent Determinism ($p = 0.006$), longer Maximum Line ($p = 0.004$), and increased Entropy ($p = 0.006$), and significantly less complex Most Commonly Used Frequency Ratio

($p = 0.007$), relative to controls (see Table 1 for model adjusted means). After controlling for group, a one unit increase in rating of perceived exertion was significantly associated with a 0.06 decrease in Entropy ($p = 0.03$). There was a significant interaction between rating of perceived exertion and group as they relate to cRQA Mean Line ($p = 0.04$). Specifically, for patients with COPD, Mean Line decreased by 0.27 with each one unit increase in rating of perceived exertion ($p = 0.01$); for control participants, Mean Line did not significantly change with increases in rating of perceived exertion ($p = 0.80$).

For models which controlled for cost of transport, patients with COPD, walking at preferred speeds, had significant increased cRQA Percent Determinism ($p = 0.0289$), longer Maximum Line ($p = 0.015$), longer Mean Line ($p = 0.0264$), increased Entropy ($p = 0.0427$), and significantly less complex Most Commonly Used Frequency Ratio ($p = 0.0017$), relative to controls (see Table 1 for model adjusted means). After adjusting for group, there were no significant associations between cost of transport and the coupling outcomes of interest.

Similar regression analysis findings were found for the slowest walking speed (−20% of preferred walking speed). After controlling for rating of perceived exertion, when walking at the slow speed, patients with COPD had a significantly less complex Most Commonly Used Frequency Ratio ($p = 0.027$) as compared to controls. This finding was also true after controlling for cost of transport ($p = 0.003$). Further, compared to controls, patients with COPD had a longer Maximum Line ($p = 0.003$).

During the fastest walking speed, regression analysis findings were similar to preferred walking speed. After controlling for rating of perceived exertion, patients with COPD had an increased cRQA Percent Determinism ($p = 0.009$), longer Maximum Line ($p = 0.017$), longer Mean Line ($p = 0.003$), and increased Entropy ($p = 0.0022$) compared to controls. After controlling for group, a one unit increase in rating of perceived exertion was associated with a 0.05 decrease in Entropy ($p = 0.025$). After controlling for cost of transport, patients with COPD had an increased cRQA Percent Determinism ($p = 0.013$), longer Maximum Line ($p = 0.024$), longer Mean Line ($p = 0.011$), and increased Entropy ($p = 0.026$) compared to controls.

DISCUSSION

The purpose of this research was to determine if efficient locomotor respiratory coupling was compromised in a disease characterized by abnormal airflow and dyspnea, i.e., COPD. A secondary purpose was to determine if coupling was associated with reduced energy efficiency in those with abnormal airflow compared to controls. It was hypothesized that patients with COPD would demonstrate stronger, yet less complex, coupling between breathing and walking as compared to controls. Further, this coupling would be associated with increased energy expenditure as compared to their healthy counterparts. The results of this study supported these hypotheses. Overall, it was found that less complex frequency ratios were associated with increased energy expenditure. Moreover, stronger coupling was associated with increased energy expenditure, as measured by cost of transport. When task demands were altered, asking subjects to walk at speeds slower and faster than their preferred walking speed, the association between energy expenditure and coupling was largely unchanged.

Persons with abnormal airflow demonstrate a less complex and stronger coupling between breathing and walking compared to healthy controls.[29,30] The results of our study are consistent with previous literature. It was found that patients with COPD used less complex frequency ratios of 1:1 and 3:2; whereas, healthy controls did not use these ratios nearly as often. Patients with COPD had stronger coupling and more variety of coupling patterns as compared to controls. Patients with COPD have a more repeatable breathing pattern and the more repeatable it becomes as disease severity increases.[27] The lack of variety within their breathing pattern may influence their ability to explore a more complex coupling between breathing and walking. Although not recorded in the current study, anxiety and level of consciousness[36], may affect breathing patterns. In addition, both hypocapnia and hypercapnia are associated with changes in airflow resistance. Hypocapnia does lead to changes in breathing patterns in some individuals.[37]

Initially, the current findings could be considered in contrast to findings found other pathologies such as Parkinson's disease.[38] Patients with Parkinson's disease demonstrated coupling ratios of 3:1 and 4:1; however, considering the short stride length in Parkinsonian gait, these higher coupling ratios are expected. Their steps were scattered across the breath cycle demonstrating less timing coordination between breathing and walking patterns. Additionally, Parkinson's disease affects coordination and movement, walking, while COPD affects the lungs, having more influence on breathing. Although there is a bidirectional influence or compromise between walking and breathing, the locomotor system affects coupling at a greater extent than changes in the respiratory system.[21] COPD and Parkinson's disease are not the only chronic conditions to demonstrate alterations in breathing and walking coupling. In spinal cord injury patients, an improvement in pulmonary function after locomotor training was documented.[39] In addition, a case report demonstrated that 12-weeks of body-weight-support treadmill training lead to coupling between breathing and walking despite the absence of coupling prior to training in a spinal cord injury patient.[40]

Increased energy expenditure has been well documented in patients with COPD. In the current study, when energy expenditure was normalized to distance traveled, a significant difference was seen between groups, consistent with previous literature.[32–35] Patients with COPD walked with a significantly slower walking speed as compared to controls, covering less distance during the walking trial. A recent article found that when walking at their self-selected speed, cost of transport was not different between patients with COPD and controls.[41] Although not statistically compared in this study, as speed increased, patients' with COPD cost of transport decreased; thus, selecting a speed that did not minimize energy expenditure. Instead, patients with COPD select the "highest speed at dyspnoea sensation is tolerable."[41] (p.6) Surprisingly, when asked to walk at the same speed (3.2 km•h^{-1}), cost of transport was not different between groups, suggesting the cost of increased ventilation is similar to healthy controls.[41]

The novel and main finding of this study was that stronger and less complex coupling was moderately associated with increased energy expenditure. This demonstrates that increased effort is needed when utilizing a frequency ratio of 1:1 or 3:2. Further, the more stable the coupling between breathing and walking, the more effort it takes. Increased variation in coupling, specifically in exploration of a multiple of frequency ratios, is related to a decrease in energy expenditure.[7] The variation in frequency ratios provides the ability to explore various coupling ratios in search for the most cost effective strategy.[7]

The more rigid a pattern, the less capable the individual is to adapt to task demands and/or the environment. With moderate coupling, the capacity to adapt is increased, as it provides the respiratory system the ability to respond to the changing demands of exercise.[6,10] Thus, if the coupling is too stable or rigid, the physiological system is unable to react to alterations in demand. Variation in breathing, movement, and other biological patterns is a hallmark of health.[42] Therefore, the ability to couple and uncouple throughout the walking trial is considered a healthy state. Both breathing and walking should mutually adjust to one another, leading to “compromise between stability and independence.”[9,43]

Although coupling between breathing and walking may be altered across walking speeds in patients with COPD,[29] the association between energy expenditure and coupling was largely unaffected at slower and faster speeds. Demonstrating that although patients with COPD may choose to walk slower, and in return have a slower respiratory rate, energy expenditure is still increased, partially due to abnormal coupling between breathing and walking. On the other hand, walking at a faster rate may not be beneficial for exercise training. As some patients in pulmonary rehabilitation use treadmill training, this may be detrimental to their training. If they have a strong coupling at a 1:1 frequency ratio, this would indicate that as speed is increased on the treadmill, respiratory rate would increase, likely increasing dyspnoea and resulting in a shorter training bout. Walking speed may not be the appropriate mode in which to increase intensity of training. Potentially other modes of exercise may allow the two systems to couple and decouple; for example, walking at a preferred speed on a slight incline or decline.[44] This is an important consideration for rehabilitation and exercise therapies applied to patients with COPD. Further, consideration of breathing and walking coupling may be given to the implementation of existing or creation of new interventions. Future studies should work to quantify the ability and frequency of coupling and uncoupling, and explore other frequency ratios, within the COPD population.

The current study has the potential to address an important unmet need in studies of COPD, namely the diagnosis of exacerbations. At present, diagnosis most commonly depends upon health care utilization. Symptom scores also have been used. Exacerbations are associated with acute deteriorations in performance and increase in symptoms. The finding from the current study provides a basis for physiologic measures that could be used to diagnose, confirm, or gauge the severity of a COPD exacerbation.

There are two limitations within this study. First, the small sample size does not reflect the heterogeneity within the presentation of COPD. Several potential phenotypes of the COPD syndrome have been identified including a clinical phenotype, physiological, radiographic, acute exacerbation of COPD, systemic inflammation, and the presence of co-morbidities.[45,46] Although all patients were screened for eligibility, it is possible that not all co-morbidities were included in the exclusion criteria. Moreover, it may be that each phenotype presents with different coupling; however, the sample size of the current study did not allow for sub-analysis. Second, rating of perceived exertion does not directly reflect energy expenditure. This is a subjective rating based on perceived exertion. However, these data supported the findings of cost of transport, an objective and direct measurement of energy expenditure. Use of other subjective scales, such as the Urge-to-Stop scale[47] may provide insight into affective modulation of task performance and provide a more comprehensive measure of perceived exertion.

In conclusion, it was found that patients with COPD have a less complex and stronger coupling between breathing and walking as compared to healthy controls. Energy expenditure, as measured by cost of transport and rating of perceived exertion, was found to be associated with coupling. In particular, the novel finding of this study was that stronger and less complex coupling was moderately associated with an increase in energy expenditure. Breathing and walking coupling should be considered when implementing interventions in patients with COPD, in order to lessen energy expenditure and the sensation of dyspnoea, and increase patients' ability to participate in activity for a longer period of time.

MATERIALS AND METHODS

Seventeen patients with COPD participated in the study (Table 2). Patients with COPD were recruited from the Pulmonary Studies Unit at the University of Nebraska Medical Center and the general population. Twenty-three healthy controls were recruited from the general population. Both groups underwent spirometry testing (MicroLoop, Vyaire Medical, Mettawa, IL) using the ratio of forced expiratory volume in one second to forced vital capacity (FEV_1/FVC) of less than 0.7[48] to confirm COPD status. Subjects from either group were excluded from the study if they reported a history of musculoskeletal, cardiovascular, or neurological disease, and/or impairment which affected walking ability. Subjects were excluded if they reported another respiratory diagnosis other than COPD and/or were taking medication that would affect metabolics. All subjects were enrolled and provided written informed consent for the study under Institutional Review Board approved procedures.

Subjects were asked to wear a tight-fitting suit (i.e., wrestling singlet) and a heart rate monitor against the skin across their chest (Polar Electro Inc., Bethpage, NY) for data collection. Subjects were asked to determine their self-selected, preferred walking speed on a treadmill.[28] Once selected, subjects were asked to rest comfortably until heart rate returned to resting levels. Retro-reflective spherical markers were attached to the heel of each foot. Subjects were equipped with a portable metabolic unit to measure volume of oxygen consumed, VO_2, and flow of inhalation and exhalation ($K4b^2$, Cosmed USA Inc., Concord, CA). Resting VO_2 was measured for five minutes while quietly standing. Subjects completed a six-minute walking trial at their preferred walking speed. During the last 15 seconds of the walking trial, subjects were asked to indicate their rating of perceived exertion from a 6–20 Borg scale. Subjects completed an additional two walking trials at +20% and −20% of their preferred walking speed. A minimum of five minutes rest was provided between trials.

Energy expenditure was measured via cost of transport and rating of perceived exertion. To calculate cost of transport, standing steady state energy expenditure was calculated for each subject by plotting VO_2 and assigning a sliding best fit line over a two-minute window. The average VO_2 of the 2-minute window that had a slope closest to zero was determined to be steady state. Walking trial data were then normalized to standing steady state VO_2. Cost of transport from each walking trial was quantified by converting the normalized VO_2 from mL kg^{-1} min^{-1} to J kg^{-1} sec^{-1} [49] and dividing by each subject's walking speed in m s^{-1}, resulting in J kg^{-1} m^{-1}.

For each trial, breathing and walking coupling was calculated using the anteroposterior trajectory of the retro-reflective marker (12-camera Raptor system, Motion Analysis Corp., Santa Rosa, CA; 120Hz) attached to the right heel was used for walking analysis. Breathing data, flow of inhalation and exhalation, were recorded via the portable metabolic unit (25Hz). All data were resampled to 30 Hz.

To quantify coupling frequency ratios from each trial, a custom MATLAB code (Mathworks, Inc., Natick, MA) determined how many right heel strikes occurred within each breath cycle using discrete relative phase.[7, 50] The ratio for each breath cycle was quantified. Ratios were considered coupled if the same ratio repeated for a minimum of two breath cycles, otherwise they were considered uncoupled and no ratio was assigned to that breath. The Most Commonly Used Frequency Ratio was recorded. Ratios of 1:1, 2:1, and 3:2 were considered less complex and more stable as compared to greater frequency ratios.[21,51,52]

To quantify coupling between breathing and walking over time, cRQA was used.[53–55] This procedure has previously been described in detail.[29] Briefly, both breathing and walking data were reconstructed in appropriate multi-dimensional space. The Euclidian distance between every set of points was determined. If the Euclidian distance between two points was below a set tolerance, the points were considered recurrent. A recurrent plot is a two-dimensional representation of recurrent and non-recurrent sets of points. The length of diagonal lines was determined and used to calculate Percent Determinism, Maximum Line, Mean Line, and Entropy. Percent Determinism was the percentage of points that fall on a diagonal line compared to the total number of points and represented the predictability of coupling between the two signals. A perfectly coupled, and highly predictable, data series pair would yield a value close to 100%. Maximum Line, the longest diagonal line, was the longest period during which the data series pair was coupled. A longer Maximum Line was an indication of stronger coupling. Mean Line, the average diagonal line lengths, indicated the average amount of time the data series pair was coupled. Entropy was defined as the probability that the length of a diagonal line, amount of time coupled, would be repeated throughout the walking trial. Lower values indicated greater probability (highly repeatable) and higher values indicated less probability (less repeatable). This measure was interpreted as the variety of timing patterns in which the data series pair was coupled.

For each trial (i.e. preferred walking speed, +20%, and −20%) the following analysis was completed. Means or medians, along with standard deviations or quartile values, of variables of interest were calculated separately for COPD and healthy control participants for each walking trial. Associations between energy expenditure and coupling variables were tested using Spearman correlations. Comparison of group means for demographics and speed were conducted using independent t-tests. To compare the two groups under the three speed conditions, 2 × 3 repeated measures ANOVA was used. Unadjusted differences in variables of interest between groups were calculated using Wilcoxon Rank Sum tests. Multiple linear regression models were used to assess adjusted associations between the predictor variables of group (i.e. COPD vs. Control), energy expenditure (i.e. rating of perceived exertion or cost of transport), as well as their interaction, and outcome coupling variables. Level of significance was set at alpha < 0.05. SAS software version 9.4 was used for analysis (SAS Institute Inc., Cary, NC).

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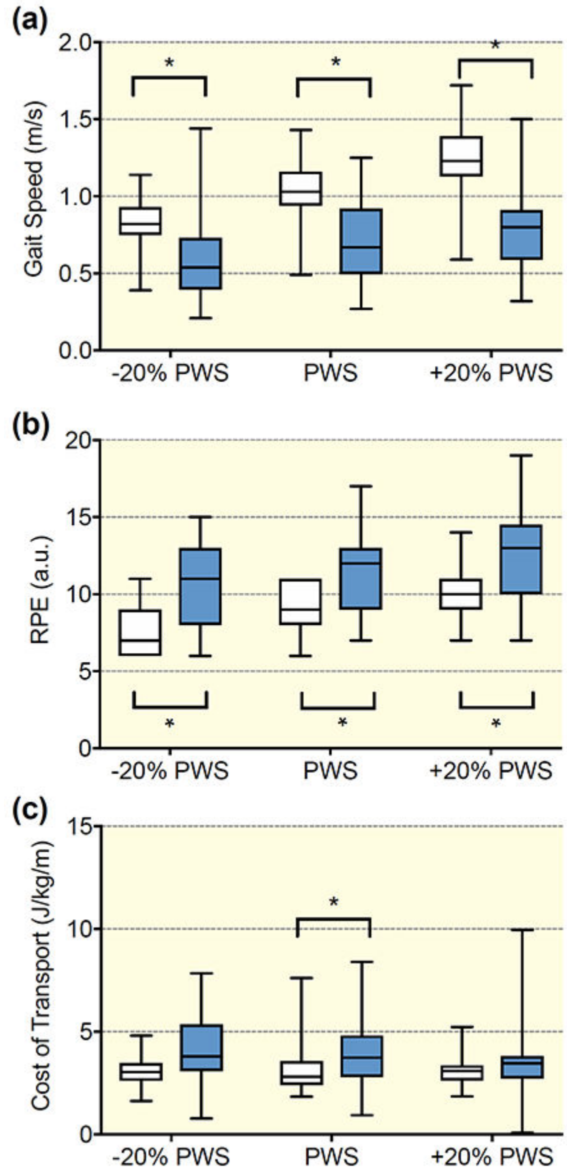


Figure 1.

Box plots of the median and quartile ranges of gait speed (**A**), rating of perceived exertion (RPE; **B**), and cost of transport (**C**). Controls are in white and patients with COPD are shown in blue. Note: PWS is preferred walking speed; * indicates $p<0.05$

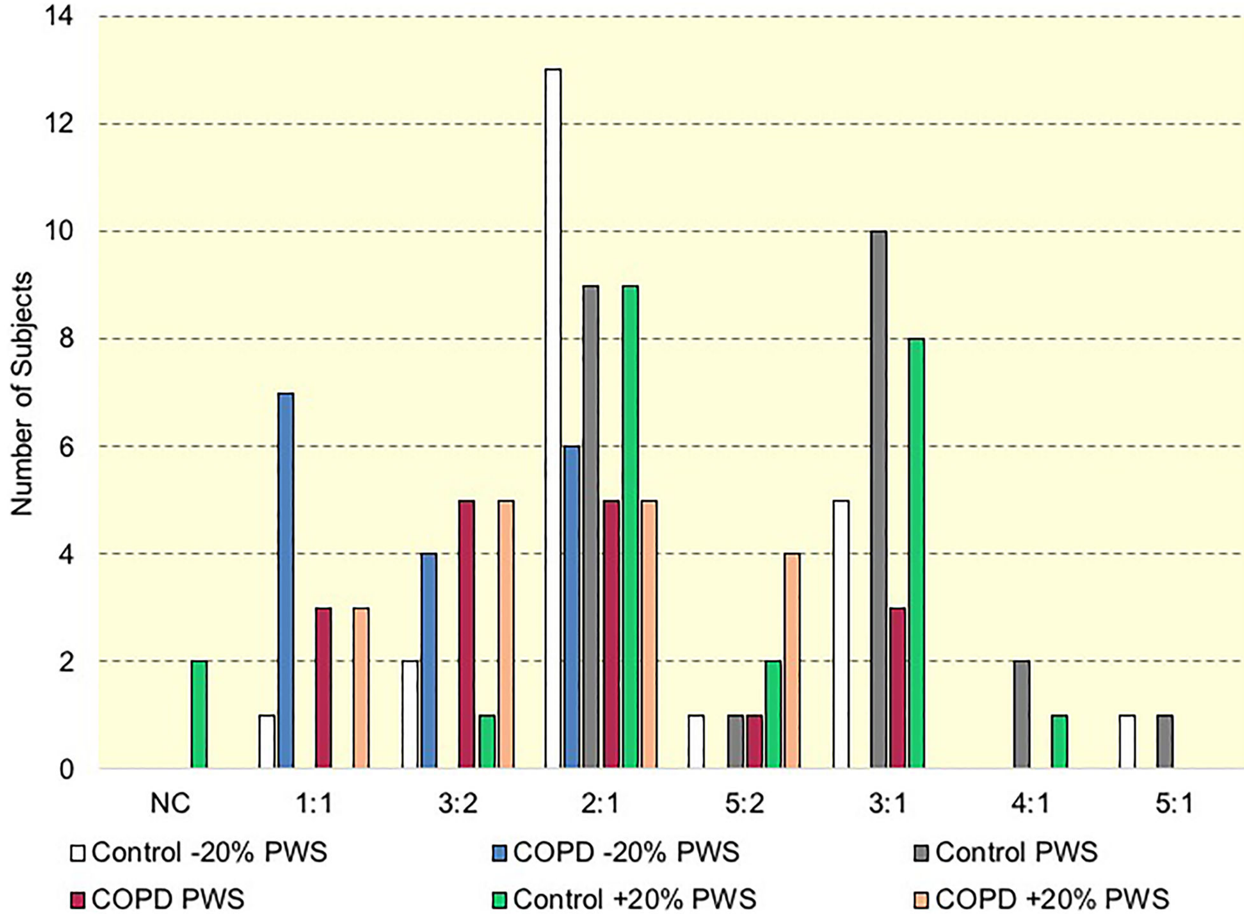


Figure 2.

The number of subjects within each group and speed that selected the ratio displayed (x-axis) as their most commonly used frequency ratio. Note: NC is no coupling; PWS is preferred walking speed

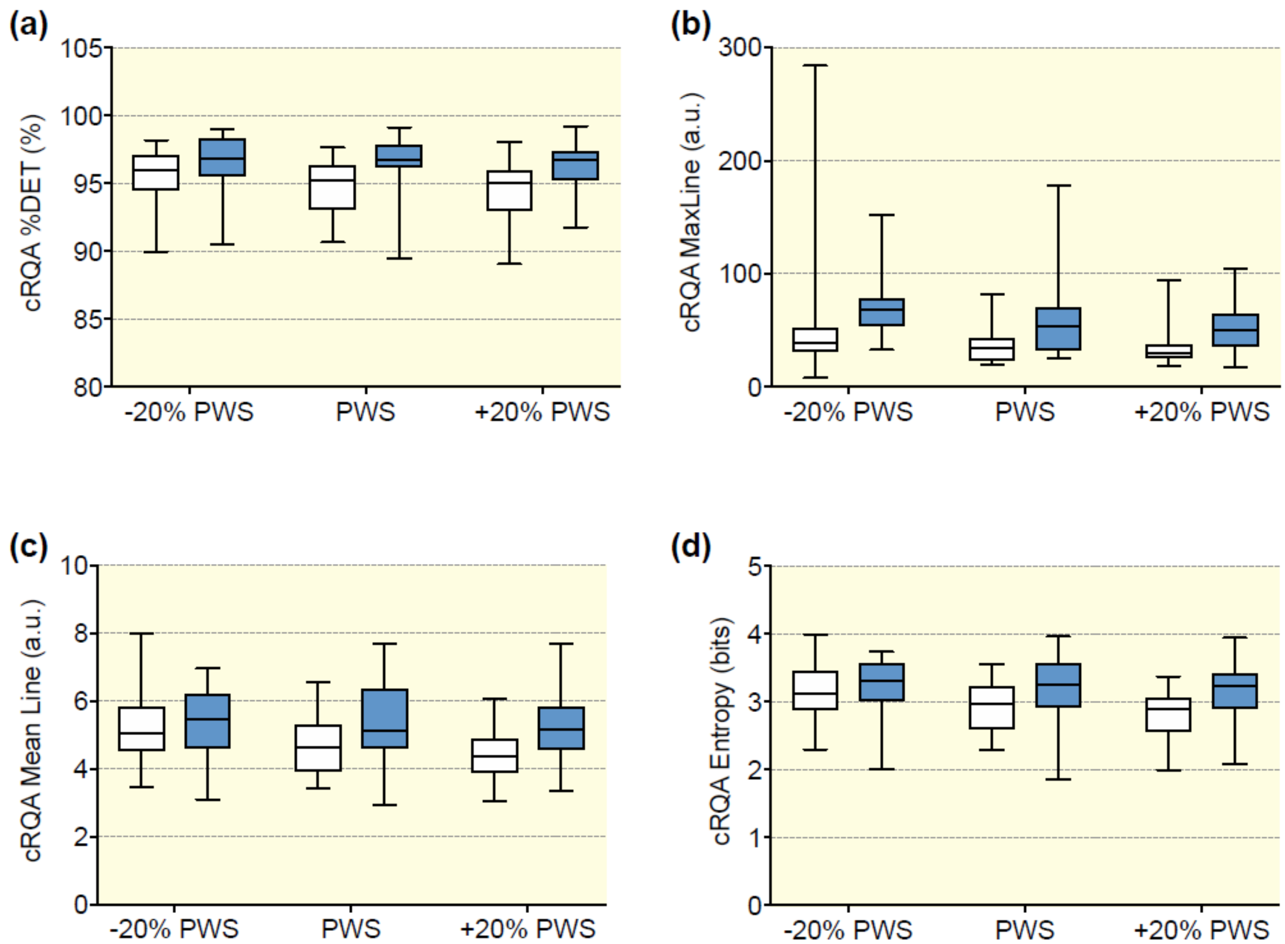
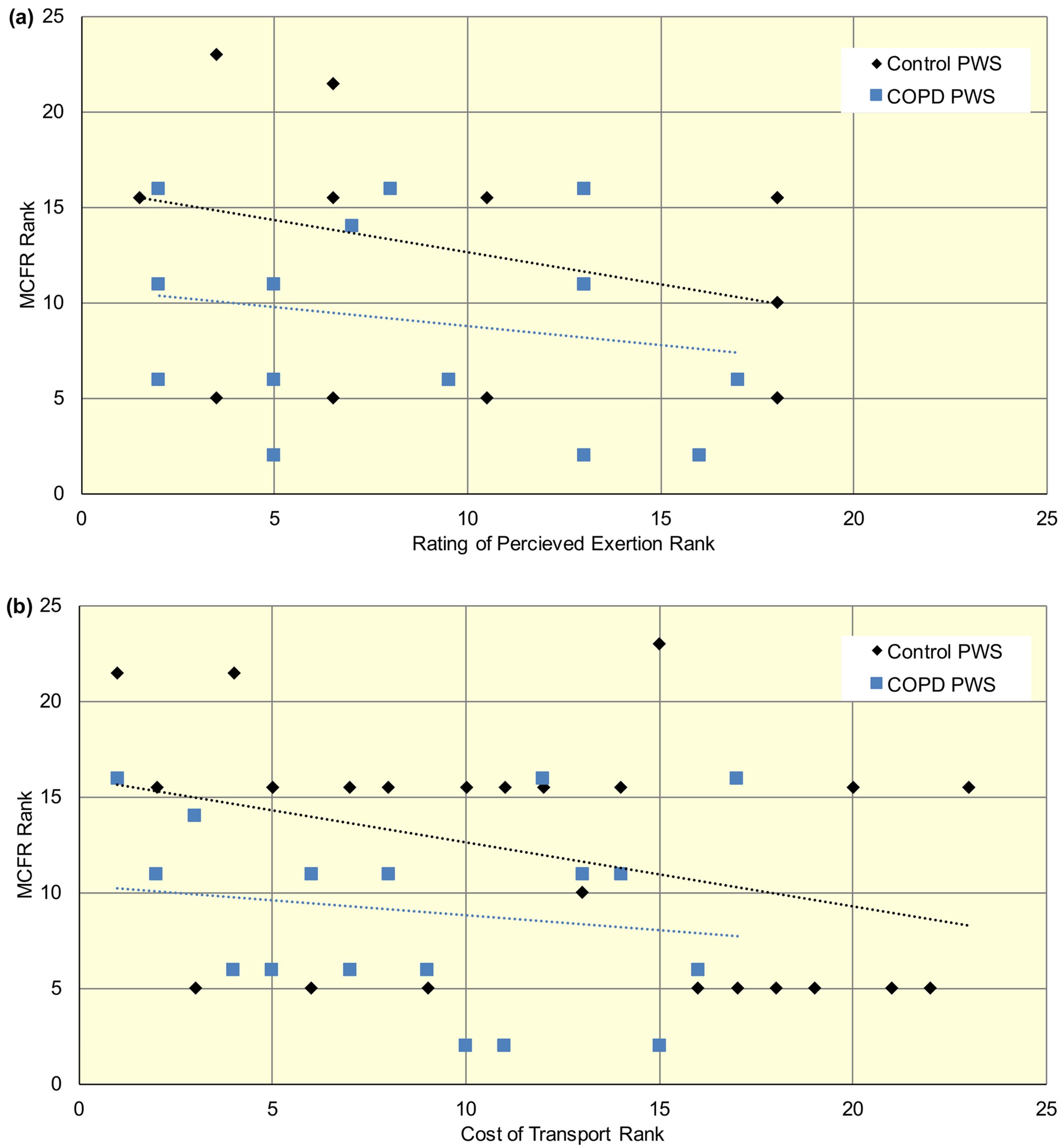
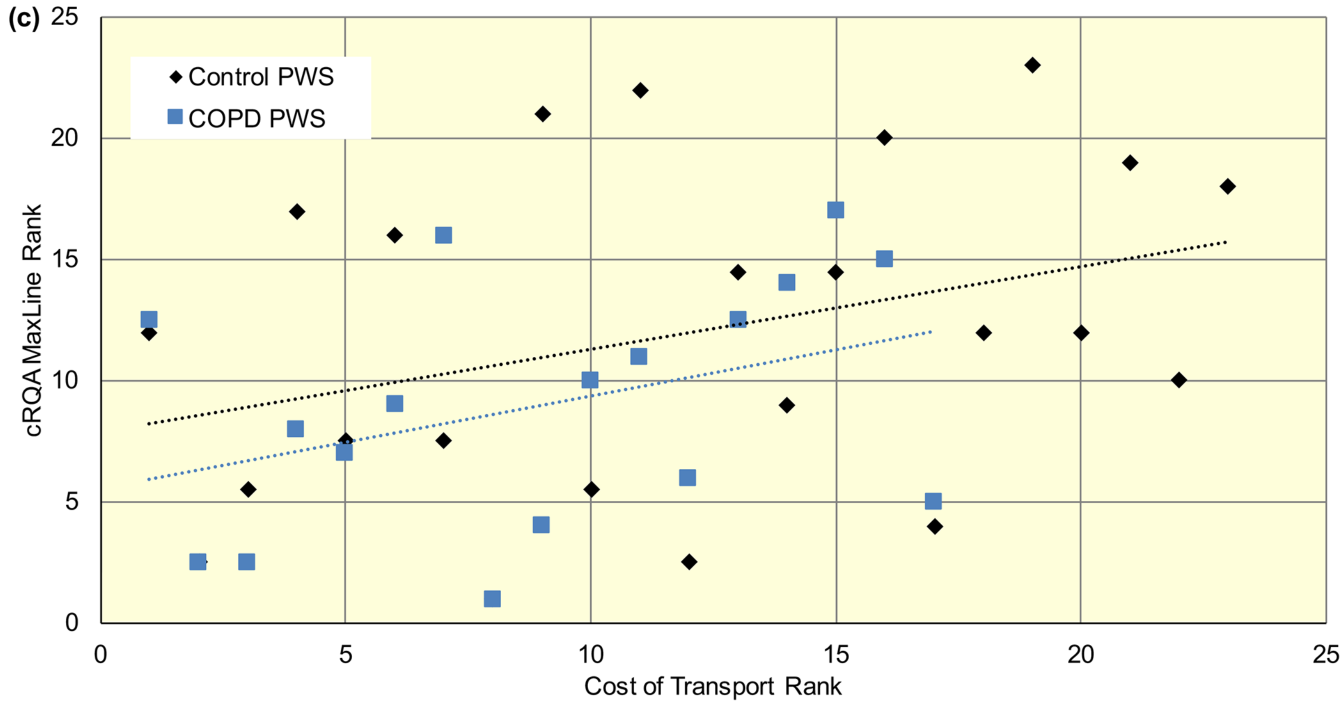
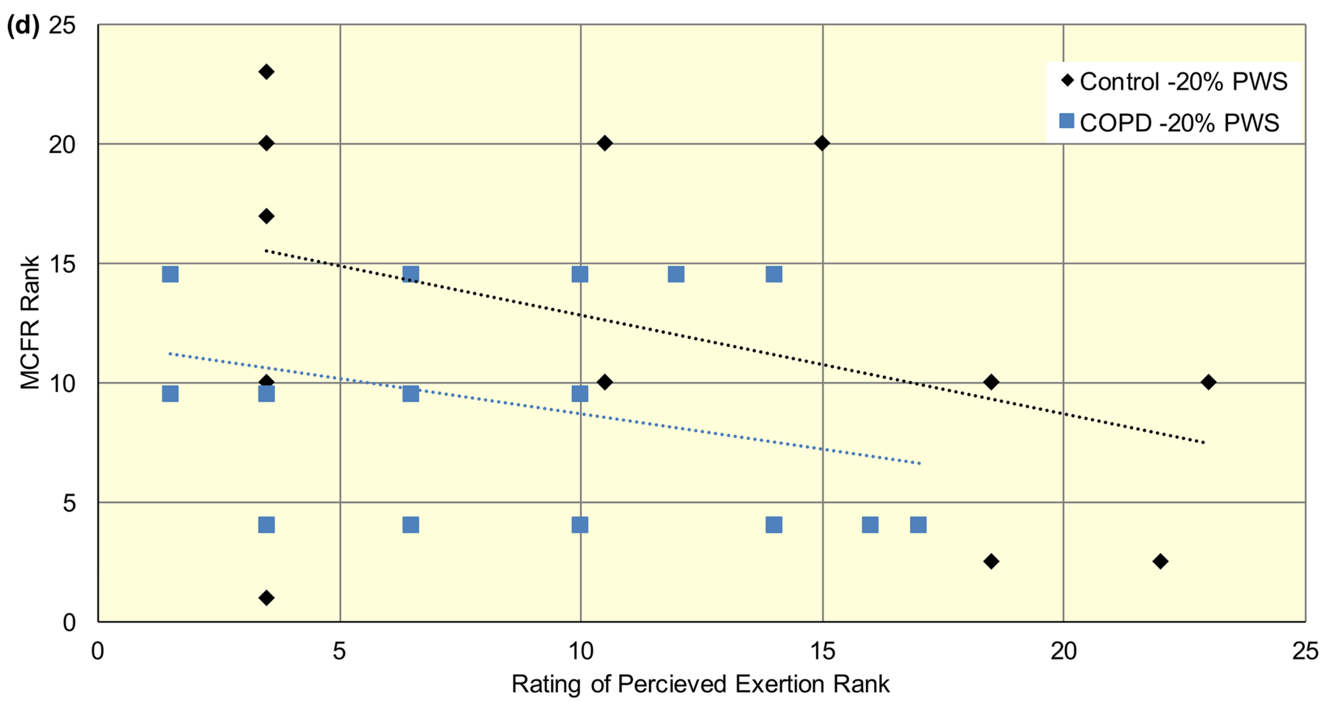


Figure 3.

Box plots of the of cross recurrence quantification analysis (cRQA) variables for controls (white) and patients with COPD (blue). Percent Determinism (%DET, **A**), Maximum Line (MaxLine; **B**), Mean Line (**C**), and Entropy (**D**) are all shown as median and quartile ranges. Note: PWS is preferred walking speed


(a)
Control PWS
COPD PWS
MCFR Rank
Rating of Percieved Exertion Rank
(b)
Control PWS
COPD PWS
MCFR Rank
Cost of Transport Rank


(c)
Control PWS
COPD PWS
cRQA MaxLine Rank
Cost of Transport Rank
0
5
10
15
20
25


(d)
Control -20% PWS
COPD -20% PWS
MCFR Rank
Rating of Percieved Exertion Rank
0
5
10
15
20
25

Author Manuscript
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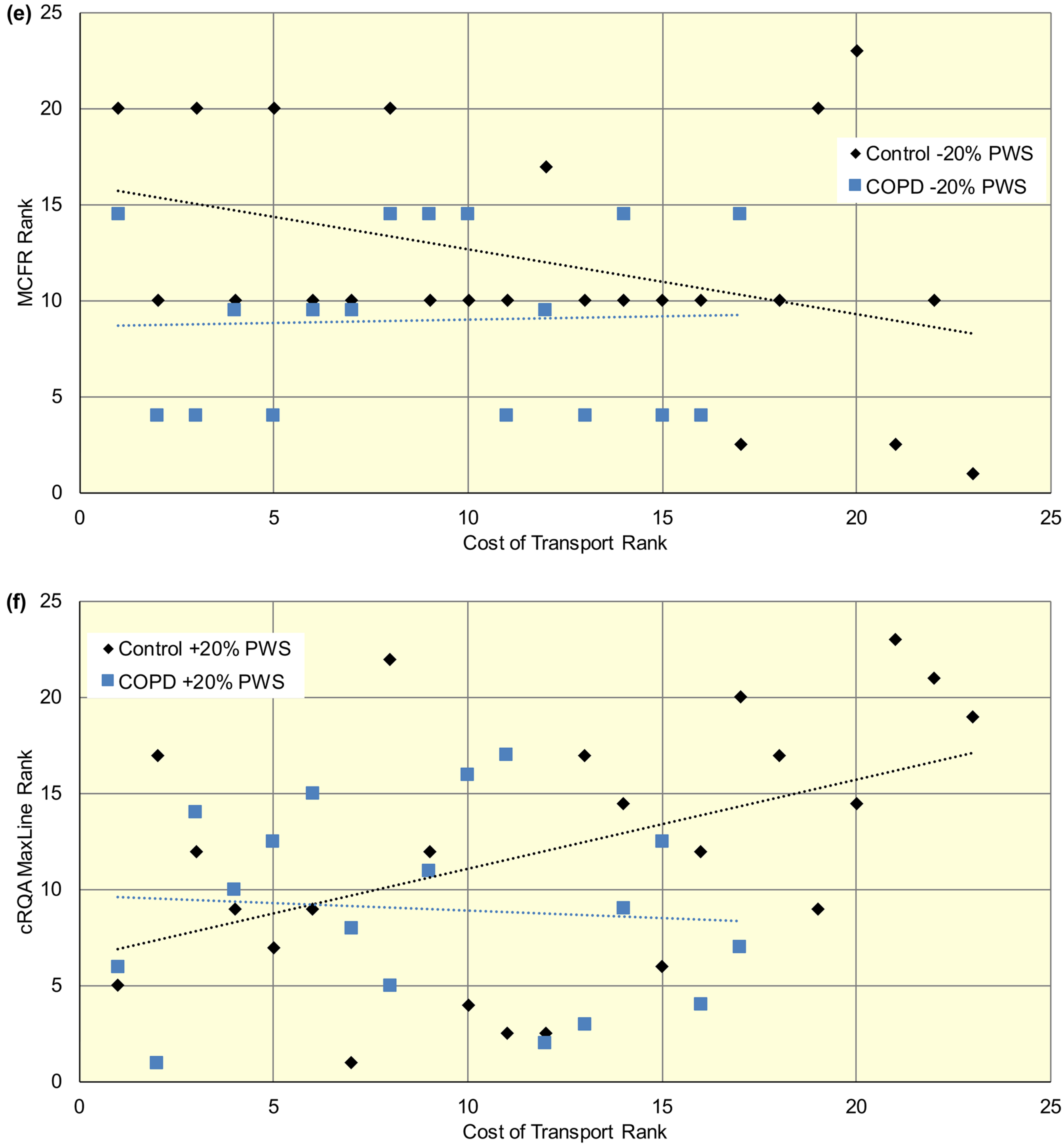

Figure 4.
Significant Spearman rho rankings with controls represented as black diamonds and patients with COPD as blue squares. At preferred walking speed a more complex frequency ratio had a moderate, inverse association with perceived exertion ($\rho = -0.38$; **A**) and cost of transport ($\rho = -0.40$; **B**). In addition, at preferred walking speed, a longer cRQA Maximum Line was

moderately associated with increased cost of transport (ρ= 0.47; **C**). At −20% of preferred speed, a more complex frequency ratio had a moderate, inverse association with perceived exertion (ρ= −0.48; **D**) and cost of transport (ρ = −0.38; **E**). At +20% of preferred speed, a longer cRQA Maximum Line was moderately associated with an increased cost of transport (ρ = 0.31; **F**). Note: Although trend lines are shown for both groups separately, reported Spearman rho value represents both groups combined. PWS is preferred walking speed; MCFR is most commonly used frequency ratio; cRQA is cross recurrence quantification analysis

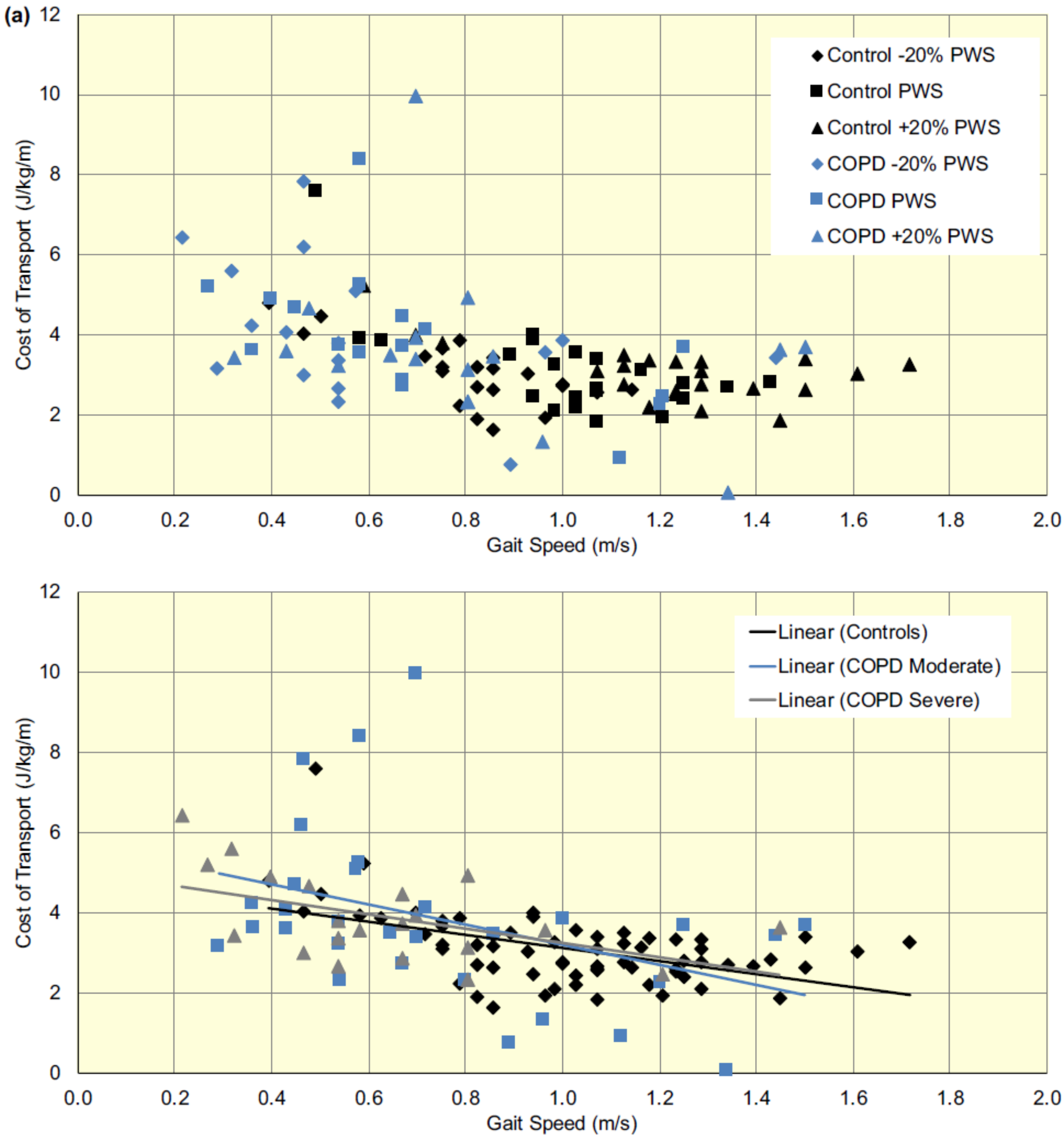

Figure 5.

A) Relationship between gait speed and cost of transport by speed conditions in controls (black) and patients with COPD (blue). −20% preferred walking speed (PWS) is represented by diamonds, preferred speed by squares, and +20% preferred walking speed by triangles. **B**) Relationship between gait speed and cost of transport by COPD lung function (FEV_1 %predicted). Controls are represented as black diamonds, patients with moderate

COPD are represented as blue squares, and patients with severe COPD are represented with gray triangles. All speeds are plotted for each group.

Table 1

Model adjusted means(standard error) for significant main effects of group at preferred walking speed. Significant p-values (< 0.05) are bolded.

	COPD	Control	P-value
Outcome, Adjusted for Rating of Perceived Exertion			
Most Commonly Used Frequency Ratio	1.98 (0.18)	2.69 (0.16)	**0.007**
cRQA Percent Determinism	96.66 (0.51)	94.65 (0.43)	**0.006**
cRQA Maximum Line	66.97 (7.76)	34.15 (6.60)	**0.004**
cRQA Entropy	3.30 (0.10)	2.88 (0.09)	**0.006**
cRQA Mean Line* (at RPE=8)	6.30 (0.35)	4.66 (0.25)	**0.001**
cRQA Mean Line* (at RPE=11)	5.49 (0.23)	4.74 (0.27)	**0.04**
Outcome, Adjusted for Cost of Transport			
Most Commonly Used Frequency Ratio	1.90 (0.19)	2.75(0.16)	**0.002**
cRQA Percent Determinism	96.41 (0.52)	94.84 (0.44)	**0.03**
cRQA Maximum Line	63.06 (7.62)	37.04 (6.51)	**0.015**
cRQA Mean Line	5.49 (0.27)	4.66 (0.23)	**0.03**
cRQA Entropy	3.23 (0.11)	2.93 (0.09)	**0.04**

*NOTE: Part of a significant interaction with rating of perceived exertion (RPE); adjusted means are reported for the 25th and 75th percentile of rating of perceived exertion; SE = standard error.

Table 2

Group demographics and characteristics means(standard deviation). Significant p-values (< 0.05) are bolded.

	COPD N=17	**Control N=23**	**P-value**
Male gender (n)	8	6	
Age (yrs)	64.3(7.6)	60.0(6.6)	0.07
Height (m)	1.68(0.11)	1.63(0.08)	0.13
Mass (kg)	89.7(31.7)	73.7(15.9)	0.07
FEV_1 / FVC (a.u.)	.54(0.14)	.79(0.06)	**<0.001**
FEV_1 % predicted (%)	50.6(11.9)	98.4(16.2)	**0.004**
ABI (a.u.)	1.10(0.14)	1.06(0.14)	0.36
Resting heart rate (bpm) ‡	71(9)	71(13)	0.96
Resting VO_2 / kg (mL/kg/min)	3.7(0.67)	4.2(0.45)	**0.003**
−20% Preferred VO_2 / kg (mL/kg/min)	9.9(2.6)	11.1(1.5)	**0.04**
Preferred VO_2 / kg (mL/kg/min)	10.9(2.4)	12.7(1.8)	**0.005**
+20% Preferred VO_2 / kg (mL/kg/min)	12.0(4.2)	14.6(2.3)	**0.009**

NOTE: ABI = ankle brachial index;

‡ indicates values have been rounded to the nearest whole number.