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**PULMONARY LIMITS TO SUB-MAXIMAL EXERCISE IN RHEUMATOID ARTHRITIS.**

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**ABSTRACT**

**PULMONARY LIMITS TO SUB-MAXIMAL EXERCISE IN RHEUMATOID ARTHRITIS. William B. Kist, Marian Minor, Andrew Mckibben, Michael W. Prewitt, Rosemary G. Hogan, Lorilie A. Weber-Hardy, Tarilyn S. Dobey, Kathryn S. Moss, Mark Wernsman, Alison Ross. JEPonline. 2003;6(2):58-69.** A pilot study was conducted to begin the process of identifying possible pulmonary mechanisms that might limit people with rheumatoid arthritis (RA) from participation in an exercise program. Two groups of females, RA (N=11) and Non-RA (N=10), performed resting and sub-maximal exercise trials. Variables included oxygen saturation (%SpO<sub>2</sub>), pulse rate, and pulmonary parameters (respiratory rate [RR], tidal volume [VT]; minute ventilation [VE]; mean inspiratory flow [VT/TI]; total time of respiratory cycle, and percentage of VT attributed to rib-cage movement) measured by respiratory-inductive plethysmography (Respirace). Subjects reported their rating of perceived exertion (RPE) and dyspnea index (Dysp-I) values. There were significant differences (p<0.05) between groups on VE at rest (RA=5.7±2.0, Non-RA = 4.9±0.8 L/min). During exercise, borderline differences were noted on ventilation-reserve, TI, VT/TI, RR, and VE. When the RA subjects were sub-categorized by presence of airway obstruction, subjects with obstruction demonstrated significantly increased Dysp-I and decreased ventilatory reserve (RA-obstructive=35%, RA=65%, and Non-RA=75%). There were no differences on %SpO<sub>2</sub> or RPE. The results of this pilot study suggest that pulmonary mechanisms probably do not limit sub-maximal exercise in RA. However, people with RA with obstructive lung disease are probably limited in performing maximal exercise by a ventilation mechanism, and by dyspnea. We intend to further investigate these preliminary findings using sophisticated exercise and pulmonary function testing equipment and methodology.

**Key Words:** Ventilation, Control of breathing, Aerobic, Respiratory-inductive plethysmography.

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## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that effects multiple organ systems and causes joint pain, stiffness, swelling, and loss of function (1). People with RA demonstrate limited range of motion, decreased muscle strength, abnormalities in gait and posture, and general de-conditioning (2). Women with RA are effected approximately three times as often as men, and life expectancy in females is shortened up to three years (3).

The efficacy of exercise in RA has been evaluated and aerobic exercise is considered an important component of RA treatment (4). Exercise can improve range of motion, strength and endurance without exacerbation of disease or joint symptoms. Current research indicates that people with RA can safely participate in conditioning exercise programs to improve their heath and fitness.

A common goal of exercise programs is to improve quality of life by enhancing personal independence. Personal independence can be enhanced by increasing maximal oxygen consumption ( $VO_{2max}$ ). In people with RA, deficits of up to 40% in  $v$  have been reported, thus, increasing  $VO_{2max}$  is both a goal and a mechanism that should increase personal independence in people with RA (5).

Although studies demonstrate a low  $VO_{2max}$  in people with RA, other studies have reported that oxygen consumption ( $VO_2$ ) at sub-maximal work loads were 30 to 50% greater for people with RA compared with controls (6). While the causes of this are relatively unexplored, gait inefficiencies, general de-conditioning, or even an increased resting metabolic rate might be causal (7). In addition, RA-related pulmonary disease should cause breathing inefficiencies, thus, RA-related pulmonary disease may explain the increased  $VO_2$  at sub-maximal exercise levels. Consistent with a pulmonary cause is that many people with RA report dyspnea, or the subjective perception of breathlessness, as a reason for stopping exercise. Since dyspnea as a cause of terminating sub-maximal exercise is abnormal, it is likely that dyspnea is a symptom of pulmonary dysfunction (8).

Fifty percent of people with RA manifest some form of pulmonary dysfunction, either obstructive or restrictive (9). Restrictive disorders include diseases of the chest wall, pleura, and lung parenchyma. Obstructive lung disorders are more prevalent in RA and include diseases of both the large and small airways (10). Pulmonary vascular disease associated with RA may also contribute to dysfunction as well as well as drug-related effects and tobacco abuse (8,9).

Pulmonary dysfunction may limit exercise in RA by several mechanisms. First, people with RA may not be able to increase ventilation to meet metabolic demands due to either restrictive or obstructive impairments. Second, people with RA with either restriction or obstruction that can increase ventilation may experience an increased work of breathing. Third, ventilation-perfusion mismatching or a diffusion defect might cause arterial oxygen desaturation. Fourth, altered ventilatory-drive, caused by increased afferent input to the brainstem from lung and chest wall receptors might be a factor (8, 11,12). Finally, these cited mechanisms could cause dyspnea that limits exercise (13). To our knowledge, no systematic investigation has been conducted to determine how pulmonary system impairments may limit exercise in people with RA. A pilot study was conducted to begin the process of identifying possible pulmonary mechanisms that might limit people with rheumatoid arthritis's participation in an exercise program.

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## METHODS

Two groups of subjects were recruited (subject characteristics are listed in Table 1). The first group consisted of females (N=11) with a confirmed diagnosis of RA (RA group). These subjects were recruited from another RA study (“A controlled study of the effects of self efficacy training on exercise beliefs and outcomes and women with arthritis in a community setting”) that was being performed at the University’s School of Health Professions (funding, see Acknowledgements). The second group consisted of healthy females (N=10) without RA (Non-RA group) that were recruited from the School of Health Professions. Both groups of subjects were recruited via word of mouth. It was attempted to match groups on subject characteristics, however, the RA group was older. This study was approved by the IRB of the University.

**Table 1. Subject characteristics and resting (supine) parameters (Trial 1)**

| <i>Parameter</i>                                     | <i>Non-RA</i> | <i>RA</i> | <i>P value</i> |
|--|---------------|-----------|----------------|
| Group size (N)                                       | 10            | 11        |                |
| Age (years)  | 48±7.2        | 59±7.6    | 0.002*         |
| Body mass index (BMI, kg/m <sup>2</sup> )            | 23.7±2.95     | 27.0±4.3  | 0.120          |
| Smoking history (pack-years)                         | 0±0           | 9.4±11.8  |                |
| Forced vital capacity - % predicted (FVC %)          | 107.9±7.6     | 98.8±15.1 | 0.102          |
| Forced expired volume-1-s/FVC (Fev1/FVC %)           | 76.8±7.9      | 73.9±10.9 | 0.485          |
| Oxygen saturation percentage (%SpO <sub>2</sub> , %) | 97.3±1.7      | 95.4±3.6  | 0.138          |
| Heart rate (beats/min)                               | 69.4±11.3     | 66.7±8.1  | 0.532          |
| Dyspnea index value (Dysp-I, 1-4)                    | 1.0±0.0       | 1.0±0.0   |                |
| Rating of perceived exertion (RPE, 6-20)             | 6.0±0.0       | 6.1±0.3   | 0.331          |
| Respiratory rate (RR, breaths/min)                   | 12.8±3.2      | 14.0±4.9  | 0.203          |
| Tidal volume (VT, mL)                                | 392.4±105.7   | 471±286   | 0.072          |
| Minute ventilation (VE, L/min)                       | 4.9±0.8       | 5.7±2.0   | 0.006*         |
| Mean inspiratory flow rate (VT/TI)                   | 216±40        | 282±133   | 0.147          |
| Inspiratory time to total time ratio (TI/TTOT)       | 0.38±0.03     | 0.37±0.04 | 0.394          |
| Inspiratory time (TI, s)                             | 1.87±0.50     | 1.69±0.56 | 0.455          |
| Ribcage to tidal volume ratio (RC/VT, %)             | 53.9±13.3     | 48.5±15.7 | 0.407          |

Non-RA, female subjects without rheumatoid arthritis; RA, female subjects with RA; Values reported are means±SD. Asterisk (\*) indicates statistical difference (p<0.05), by group, via independent samples t-test.

Subjects without cardiovascular disease, chronic obstructive pulmonary disease (COPD), a clinically significant smoking history, that is a volume of smoking that typically does not compromise important pulmonary function markers (e.g. a 30 pack year history should reduce the forced expiratory volume only 6%), thyroid disease, medication usage that influenced resting metabolic rate, and unacceptable “readiness for exercise” (Par-Q) findings were included (9,14,15). Non-RA subjects were excluded if they would be considered “trained” aerobic exercisers (Non-RA subjects were either sedentary or “recreational exercisers”). Non-RA subjects were also excluded if they had abnormal Spirometry values (MultiSPIRO Incorporated, Tempe, AZ) (16). Body mass index (BMI) was calculated from measured height and weight (Continental Scale Works, Chicago IL) (17).

Subjects performed four serial trials. The first trial in the series was a “supine-resting” trial (baseline) in which the subject relaxed in a recliner in a semi-recumbent position for 20 minutes, with only the last ten minutes of data analyzed (Table 1). The second trial, a pre-exercise “standing-resting” trial required subjects to stand on a treadmill for four minutes. The third trial, “sub-maximal exercise” trial, required an initial four minutes of walking on the treadmill at a self-selected pace at 0% grade for four minutes (warm up), followed by four minutes of sub-maximal exercise at a 5% grade at the same speed (18). Typically the subject’s heart rate was between 50 and 70% of their age-predicted maximal heart rate (approximately 50% VO<sub>2</sub>max) (8,14). For the fourth trial, the post-exercise “recovery trial,” the subject was required to stand on the treadmill for four minutes.

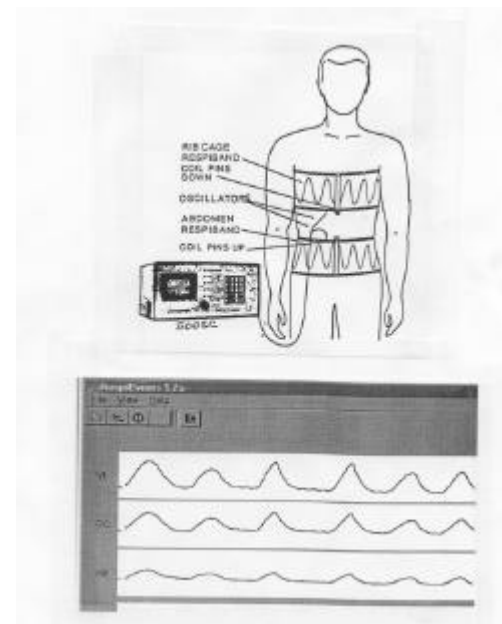
Throughout trials oxygen saturation (%SpO<sub>2</sub>), a marker of gas exchange (i.e. respiration), and heart rate (pulse rate) were measured via a motion-independent pulse-oximeter (Nellcor, N-395, Mallinckrodt Incorporated, St. Louis, MO) (19). Subjects reported their rating of perceived exertion (RPE, scale=6-20) and degree of dyspnea (Dyspnea Index, scale=1-4) using visual analog scales (Table 2) (14). Ventilation and ventilatory-drive parameters were non-invasively measured via respiratory inductive plethysmography (Respirtrace 300 SC, Non Invasive Monitoring Systems, Miami Beach, FL).

**Table 2. Rating of Perceived Exertion (RPE) and Dyspnea Index (Dysp-I) scales**

| <i>Rating of Perceived Exertion</i> | <i>Dyspnea Index</i>                             |
|-------------------------------------|--|
| 6.                                  | 1. mild, noticeable to patient, not observer     |
| 7. Very, very light                 | 2. mild, some difficulty, noticeable to observer |
| 8.                                  | 3. moderate difficulty but can continue          |
| 9. Very light                       | 4. severe difficulty, patient cannot continue    |
| 10.                                 |  |
| 11. Fairly light                    |  |
| 12.                                 |  |
| 13. Somewhat hard                   |  |
| 14.                                 |  |
| 15. Hard                            |  |
| 16.                                 |  |
| 17. Very hard                       |  |
| 18.                                 |  |
| 19. Very, very hard                 |  |
| 20.                                 |  |

The Respirtrace (as illustrated in Figure 1) is a device used to measure ventilation parameters on individuals with lung dysfunction at rest and during exercise (20, 21, 22). The Respirtrace uses inductance-plethysmography measured with two coils of Teflon-insulated gold-wires sewn into elastic bands that encircle the ribcage and abdomen (20, 21). The bands are electrically-excited by an oscillator, and changes in the cross-sectional area of the ribcage and abdomen during breathing alter the inductance of the coils and the frequency of the oscillator. Thus, via a calibration, ventilation parameters (tidal volume, VT; minute ventilation, VE; and percentage of tidal volume attributed to ribcage movement, RC/VT) were non-invasively measured on a semi-quantitative ( $\pm 10\%$  volume accuracy) basis (20, 22). The Respirtrace was calibrated using the least squares method immediately prior to data collection and its volume-accuracy was validated by comparing its derived values to those simultaneously obtained via spirometric measurement (20). Respirtrace belts were maintained in position throughout trials by taping the belts to the subject and marking their position (21).

The Respirtrace also measured time-related parameters (respiratory rate [RR]; inspiratory time [TI]; expiratory time,



**Figure 1. Illustration of Respirtrace 300 SC (with permission from Non-Invasive Monitoring Systems) attached to an individual.**

Abbreviations: AB, abdominal signal; RC, ribcage signal, and Vt, tidal volume, which is also expressed mathematically as the “sum” (ribcage compartment plus the abdominal compartment) signal.

and total time of the respiratory cycle [TTOT]). Using both the ventilation and time parameters allowed derivation of indicators of ventilatory-drive (TI, ratio of inspiratory time to total time of the respiratory cycle, TI/TTOT; and mean inspiratory flow, VT/TI). Ventilatory-drive parameters, as measured in this study, are pulmonary indicators that correlate with actual ventilatory-drive (output from the brainstem).

Data were analyzed via SPSS statistical software (SPSS Inc. Chicago, IL). Data was checked for normality, linearity, and univariate and multivariate outliers. Missing data were replaced with group means. Subject characteristics were analyzed by independent samples t-tests. Oxygen saturation, Dysp-I, and spirometric values were analyzed by independent samples t-tests to determine if there were differences between groups by smoking history. Oxygen saturation, as well as ventilation, ventilatory-drive, and respiratory parameters, were analyzed via mixed design ANCOVA (GROUP by TRIAL [repeated measures]) using age as the covariate. For some analyses, the RA group was subdivided by the presence of obstructive lung disease (FEV1.0/FVC < 70%) to form RA-subgroups (8,16). Heart rate reserve data were analyzed by ANOVA. An alpha of  $p < 0.05$  was considered significant for all tests.

## RESULTS

### **Effect of smoking history on selected exercise and pulmonary function markers.**

Selected pulmonary function, ventilation, and respiratory markers were not statistically different by smoking history: exercise-%SpO<sub>2</sub> (non-smokers=96.5±2.1 %, smokers=97.2±0.5), exercise-Dysp-I (non-smokers=1.27±0.5, smokers=1.38±0.6), FEV1.0/FVC (non-smokers=75.5±10.4 %, smokers=74.7±7.4), and FVC % predicted (non-smokers=103.2±11.2, smokers=102.8±17.2 %). Subjects with RA who had obstructive airways (RA-obs) disease smoking history was not statistically different from RA subjects (RA=9.4±11.8 pack years, RA-obs=9.0±12.7).

### **Cardio-respiratory parameters by trial and group.**

Cardio-respiratory parameters (not adjusted for age) for trials two (rest-standing, i.e., pre-exercise), three (sub-maximal exercise), and four (recovery) are shown in Table 3. Minute ventilation for these three trials was significantly higher in the RA group. During the sub-maximal exercise trial, the RA group demonstrated significantly greater RR, VT/TI and Dysp-I, and shorter TI. Mean inspiratory flow was also greater in the RA group during recovery. Heart rate was greater during recovery in the Non-RA group. Treadmill speed during sub-maximal exercise (not shown) was 2.08±0.30 mi/hr (estimated MET value=4.02) for the RA group and 2.20±0.20 (estimated MET value=4.20) for the Non-RA group.

When sub-maximal exercise parameters were adjusted for age (i.e. ANCOVA), significant differences were not observed (values subsequently presented in this paragraph are marginal means and standard errors), VT/TI (Non RA=1045±171, RA=1461±162), RPE (Non RA=9.1±0.86, RA = 10.9±0.81) and Dysp-I (Non-RA=1.23±0.16, RA = 1.36±0.15). However, two measurements, percentage of maximum ventilation used, (%VEmax, Non RA=29.1±4.9 %, RA=38.6±4.7) and TI (Non RA=1.22±0.09 second, RA=0.92±0.09) were of borderline significance ( $p=0.05$ ), while tendencies to be different were demonstrated in VE (Non RA=25.5±4.02 l/min, RA=37.5±3.8,  $p=0.07$ ) and Resp-f (Non RA=24.0±5.27 bpm, RA=38.5±5.0,  $p=0.09$ ). Power analyses for all parameters were low (<0.80).

**Table 3. Pulmonary parameters by group and trial.**

| Parameter                  | Non-RA       |                  |                  | RA           |                  |                  |
|----------------------------|--------------|------------------|------------------|--------------|------------------|------------------|
|                            | Rest Trial 2 | Exercise Trial 3 | Recovery Trial 4 | Rest Trial 2 | Exercise Trial 3 | Recovery Trial 4 |
| <i>SaO<sub>2</sub></i> (%) | 98.5±1.34    | 97.1±1.92        | 97.9±2.6         | 96.8±2.6     | 96.3±1.75        | 97.6±1.69        |
| <i>HR</i> (beats/min)      | 79.8±10.3    | 108.6±10.3       | 90.6±11.3*       | 74.8±6.9     | 101.3±7.4        | 81.1±8.8*        |
| <i>Dysp-I</i>              | 1.00±0       | 1.05±0.2*        | 1.0±0.0          | 1.0±0.0      | 1.53±0.7*        | 1.0±0.0          |
| <i>RPE</i>                 | 6.3±0.5      | 9.25±1.6         | 6.2±0.4          | 6.6±0.7      | 10.9±2.7         | 7.2±1.5          |
| <i>RR</i>                  | 4.2±3.6      | 23.2±3.5*        | 15.6±3.7         | 15.9±7       | 39.2±19.0*       | 18.7±3.3         |
| <i>VT</i>                  | 526±204      | 114.8±215        | 623±150          | 558±193      | 1116±316         | 739±189          |
| <i>VE</i>                  | 6.92±1.43*   | 25.0±4.0*        | 9.1±1.60*        | 8.8±2.0*     | 37.9±14.2*       | 13.0±3.03*       |
| <i>VT/TI</i>               | 342±104      | 1033±266*        | 442±153*         | 425±105      | 1473±574*        | 604±135*         |
| <i>TI/TOT</i>              | 0.37±0.03    | 0.44±0.03        | 0.38±0.33        | 0.36±0.04    | 0.45±0.05        | 0.37±0.05        |
| <i>TI s</i>                | 1.66±0.42    | 1.24±0.14*       | 1.59±0.33        | 1.37±0.43    | 0.89±0.31*       | 1.34±0.40        |
| <i>RC/VT</i> (%)           | 72.6±10.2    | 65.1±12.2        | 72.4±9.4         | 71.4±19.5    | 62.1±19.6        | 74.0±17.4        |

Non-RA, subjects without rheumatoid arthritis (RA); RA, subjects with RA; rest, rest trial (standing); recovery, post-exercise (standing); %SaO<sub>2</sub>, percentage of oxygen saturation; HR, heart-rate in beats/min; Dysp-I, dyspnea index; RPE, rating of perceived exertion, RR, respiratory rate in breaths/min.; VT, tidal volume in ml; VE, minute ventilation in L/min; VT/TI, mean inspiratory flow; TI/TOT, duty cycle; TI, inspiration time in seconds; and RC/VT, percentage of VT attributed to rib cage movement. Values reported are means±SD. Asterisk (\*) indicates statistical difference (p<0.05) via independent samples t-test between groups on given trial.

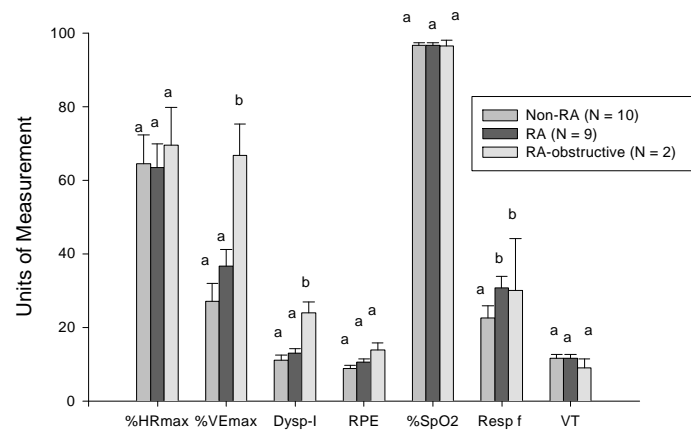
### Age-adjusted cardio-respiratory parameters by sub-group with exercise.

Age adjusted cardio-respiratory parameters (estimated marginal means and standard errors) compared by sub-group are illustrated in Figure 2. The Dysp-I was significantly greater in the RA-obstructive subgroup compared to the other groups. The RA-obstructive subgroup had a smaller ventilatory-reserve during exercise compared with the other groups. Both the RA and RA-obstructive groups had significantly higher RR than the Non-RA subjects during exercise. Power analyses, other than for the Dysp-I, were less than 0.80: percentage of heart rate reserve=0.45, percentage of ventilatory-reserve=0.44, RPE=0.43, %SpO<sub>2</sub> = 0.05, RR=0.25, and VT=0.13.

## DISCUSSION

The purpose of this study was to begin the process of identifying possible pulmonary mechanisms that might limit people with rheumatoid arthritis's (RA) participation in an exercise program. These findings suggest that pulmonary factors probably do not limit sub-maximal exercise in people with RA. However, based upon the current findings, people with RA and airway obstruction, would be limited in performing high intensity aerobic exercise, and high intensity exercise may be contraindicated. Due to the fact that there were significant

Age-adjusted cardio-respiratory parameters by group (subgroup).



**Figure 2. %HRmax, percentage of maximum heart rate utilized; %VEmax, percentage of maximum ventilation utilized; Dysp-I, dyspnea index \* 10<sup>-1</sup>; RPE, rating of perceived exertion; %SpO<sub>2</sub>, percentage of oxygen saturation; Resp-f=RR (breaths/min); and VT (tidal volume, mL x 10<sup>2</sup>). Values are means±Standard errors. Values with different superscripts are statistically different (p<0.05) by ANCOVA.**

differences between groups on age (Table 1), the effect of age must be addressed in the interpretation of this pilot study.

#### **Effect of age on ventilation, ventilatory-drive, and respiratory parameters at rest.**

It is known that aging increases lung compliance, airway resistance, ventilation-perfusion mismatching, and some lung volumes (23). Further, aging decreases respiratory muscle strength, and the ventilatory response to increased carbon dioxide and decreased oxygen concentrations is blunted (16,23). Despite these known pulmonary effects, resting ventilation values are typically not different between young and old adults (24,25). The probable explanation for this is that the decreased efficiency of the older individual's pulmonary system is offset by changes in body composition and decreases in metabolic rate, thus yielding similar pulmonary values under resting conditions (7,17). Since VE (Table 1) was statistically different between the groups (Non-RA=4.9±0.8 L/min., RA=5.7±2.0), this leads us to suspect that RA, not age, was likely responsible for the increased resting VE (24,25).

#### **Effect of age on sub-maximal exercise parameters.**

In contrast to resting values, a paucity of literature exists that supports that age does affect pulmonary parameters during exercise (25). Teramoto et al., using respiratory inductive plethysmography during sub-maximal exercise (approximately 50% VO<sub>2</sub>max), observed that older subjects (71.9±5.3 yrs) demonstrated VE values that were approximately 25% greater, RR 40% greater, while VT and RC/VT were approximately 10% smaller than younger subjects (25.0±4.9 yrs). Since age probably affects ventilation responses with exercise, we used ANCOVA analysis, with age as the covariate, to compare the groups.

When the values depicted in Table 3 were analyzed via ANCOVA, only borderline differences and tendencies to be different between RA and Non-RA groups were observed. However, as previously stated, power analyses for all values parameters were considerably less than the ideal power level of 0.80, thus, ventilation and ventilatory-drive parameters probably would have been significantly different between RA and non-RA subjects if the present study had greater power. This makes it likely that the significant differences depicted in Table 3 should probably not be ignored.

#### **Sub-maximal exercise parameters: effect of obstructive airway disease.**

As illustrated in Figure 2, although subjects exercised to approximately the same exercise intensity (60-70 % of their maximal heart rate), RA-obstructive subjects were utilizing a significantly greater percentage of their ventilatory-reserve (% VEmax). Had exercise continued to maximal intensity, the RA-obstructive subjects would have reached a ventilation limitation to exercise, consequentially limiting exercise (and reducing VO<sub>2</sub>max). This ventilation response to exercise contrasts with normal individuals, who demonstrate a large ventilatory-reserve, even at VO<sub>2</sub>max (8,14,26). Thus, it can be concluded that people with RA with obstructive airways disease are limited in performing maximal exercise by a pulmonary mechanism. However, this conclusion was weakened by the small number (N=2) of RA-obstructive subjects in this pilot study.

Another difference demonstrated by the RA-obstructive individuals was an increased Dysp-I (Figure 2).

Although none of the RA-obstructive subjects of the present study requested to stop exercise due to dyspnea, it is probable that had exercise continued to higher levels, dyspnea may have become a limiting factor. Breathing at a high percentage of one's maximal ventilation ability is known to cause dyspnea (11, 26, 27). While the RA-obstructive individuals may have experienced dyspnea because of a low ventilatory reserve, the etiology of dyspnea is typically multi-factorial (13).

Another factor that may have contributed to the increased dyspnea in the RA-obstructive individuals was the work of breathing. In individuals with obstructive lung disorders the work of breathing contributes to dyspnea and can limit exercise (26). In persons with normal lungs, under resting conditions less than 5% of VO<sub>2</sub> goes toward the work of breathing, while during exercise approximately 30% of the VO<sub>2</sub> goes toward the work of breathing (27). In contrast, in persons with obstructive lung disease, greater than 15% of total resting VO<sub>2</sub> goes toward the work of breathing, while during exercise a huge percentage of the total VO<sub>2</sub> consumed can go to the

work of breathing, and consequentially limit exercise (23). While work of breathing was not measured in this pilot study, the presence of obstructive lung disease makes the work of breathing a probable contributor to the dyspnea (8,13,23).

Other factors contributing as a source of dyspnea in the RA-obstructive subjects seem less probable. Respiratory muscle fatigue is a less likely source of dyspnea as the duration of exercise was brief. However, it has been demonstrated that people with RA do manifest respiratory muscle weakness (28). Thus, it is possible that the RA-obstructive subjects had respiratory muscle weakness or fatigue that contributed to the dyspnea. Likewise, arterial oxygen desaturation is not a likely a factor contributing to dyspnea in the RA-obstructive subjects (Figure 2) as RA-obstructive subjects %SpO<sub>2</sub> values during sub-maximal exercise were not different from the other groups. However, because of the sigmoid shape of the oxygen-dissociation curve, it is possible that mild hypoxemia occurred without a detectable change in %SpO<sub>2</sub> (9).

### **Ventilatory-drive in RA**

The fact that RR during exercise was significantly increased in both RA and RA-obstructive groups (Figure 2), and tendencies for RR, VT/TI, and TI to be different between RA and Non-RA subjects (ANCOVA of data in Table 3), suggests that people with RA may have an altered ventilatory-drive (control of breathing) during exercise. The significantly different VT/TI, TI, and RR between RA and Non-RA subjects (Table 3) during exercise also supports the likelihood of an altered ventilatory-drive in RA subjects.

Limited contradictory ventilatory-drive information exists in people with RA (28, 29). In one study, ventilatory-drive was increased while in another study ventilatory-drive was found to be normal or even diminished. Neither of these investigations studied RA subjects during exercise. Prospectively, it was hypothesized that RA subjects might demonstrate increased ventilatory-drive during exercise via several mechanisms: 1) increased resting metabolic rate, 2) anemia, 3) desaturation with exercise, or 4) pulmonary disease that effects lung or chest-wall receptors to stimulate the brainstem (7,9,10).

Several potential mechanisms as a source of a probably altered ventilatory-drive in the RA group can be excluded by the findings of the present investigation. The lack of differences between groups on resting ventilatory-drive indicators (RR, VT/TI, TI, and TI/TTOT) of Table 1 do not support that an increased resting metabolic rate was a mechanism of the increased ventilatory-drive. Likewise, %SpO<sub>2</sub> data during exercise (Figure 2) would not support hypoxemia as the explanation for the tendency to have an increased ventilatory-drive. Hypoxia, via an anemia mechanism, also seems an unlikely source of the tendency of an increased ventilatory-drive in RA subjects as the amount of cardiac work in the RA groups were comparable to the Non-RA subjects. It seems likely that if the RA subjects of the present study had anemia, a reduced oxygen carrying capacity of blood, this would have been manifested by increased cardiac work. Finally, although RA subjects did not differ from Non-RA subjects on RC/VT (Tables 1 and 3), this finding does not rule out that RA subjects may have increased input to the respiratory centers. Thus, increased input to the respiratory centers remains the most likely hypothesis explaining the suggested increased ventilatory-drive of the present investigation. An investigation utilizing a more direct measure of ventilatory-drive is recommended to further investigate ventilatory-drive in people with RA (28).

The findings of this pilot study are limited by the small number of RA subjects with obstructive lung disease (N=2) or restrictive lung disease (N=0) that we were able to recruit, and low statistical power. The generally insignificant differences between groups on pulmonary system parameters were probably related to our low levels of power. The semi-quantitative ability of respiratory inductive plethysmograph also may have limited our ability to detect small, but meaningful differences in function of the respiratory system between RA and Non-RA groups. Thus, it would be of great value to perform an investigation using large numbers of people with RA, including those with normal lungs, and obstructive and restrictive impairments, using sophisticated exercise (gas exchange exercise testing, exercise-spirometry, occlusion pressures, etc.) and pulmonary function

tests (diffusion capacity, airway resistance, work of breathing, respiratory muscle forces, etc.) to more accurately measure pulmonary system parameters. We intend to conduct such a study.

### Conclusion

In conclusion, exercise at low or moderate intensity in people with RA appears safe to perform without the need for %SpO<sub>2</sub> monitoring or pulmonary function measurements. The results of this pilot investigation suggest that people with RA with obstructive airways disease are limited by ventilation mechanisms in performing high levels of aerobic exercise. RA-obstructive individuals may also be limited in performing high levels of aerobic exercise via dyspnea. RA subjects, with or without obstructive airways disease, demonstrated tendencies to breathe with an increased ventilatory-drive during sub-maximal exercise. We intend to pursue further investigation into pulmonary limitations to exercise in people with RA is needed using sophisticated exercise and pulmonary function technology and a larger sample size.

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**APPENDIX****Ventilation parameters (markers related to the mechanical properties of the chest wall and lungs).**

|                 |   |
|-----------------|---|
| FEV1.0          | Forced expiratory volume in one second, is the volume of air (liters) exhaled during the first second of a forced vital capacity maneuver.  |
| FVC             | Forced vital capacity, is the maximum volume of air (liters) exhaled during a forced exhalation that was preceded by a maximal inspiration to total lung capacity.  |
| FEV1.0/FVC      | Ratio of the FEV1.0 to FVC, a value less than 70% <u>confirms</u> obstructive airways disease.  |
| FVC % predicted | Comparison of actual FVC to predicted FVC. A FVC % predicted value of less than 80% <u>suggests</u> pulmonary restriction.  |
| Resp-f or RR    | Respiratory rate, the number of breaths, or breathing cycles per minute.  |
| VT              | Tidal volume, the volume of air (milliliters) inspired or expired with each breath.   |
| VE              | minute ventilation, the amount of air (liters) exhaled each minute. Minute volume is sometimes calculated as the average (mean) $VT * RR$ ( $VE = VT * RR$ ).   |
| RC/VT           | Ribcage to tidal volume ratio, is the percentage of VT attributed to ribcage movement.. Percentage varies with body position (upright greater than supine) and gender. Typically females have a greater percentage of the VT attributed to ribcage movement than males.   |
| % VEmax         | Percentage of exercise VE to maximum VE. That is, the ventilatory reserve. Normal individuals never reach a $VE/VEmax$ value close to 100% even at maximal exercise. Maximum VE is typically estimated as $FEV1.0 * 40$ ( $VEmax = FEV1.0 * 40$ ) or the maximum voluntary ventilation (MVV) value is considered the VEmax value. |

**Ventilatory-drive (sometimes referred to as “control of breathing”) parameters in this article are actually markers of respiratory pattern that correlate with ventilatory-drive.**

|         |   |
|---------|---|
| TI      | Inspiratory time, is the time (seconds) required to inspire a breath.   |
| VT/TI   | Mean inspiratory flow, is the VT (milliliters) divided by the TI (seconds). Greater values indicate a greater demand to breathe (greater air hunger).   |
| TI/TTOT | Is the ratio of inspiratory time (seconds) to the total time (seconds) of the respiratory cycle (total time = inspiratory time plus expiratory time). TI/TTOT is sometimes called the duty cycle. |

**Respiratory parameters (marker of gas exchange in the lung).**

|                   |  |
|-------------------|--|
| %SaO <sub>2</sub> | Oxygen saturation, the percentage of hemoglobin loaded with oxygen versus its maximal carrying capacity. Values less than 88% are dangerous and require administration of supplemental oxygen. Respiration values reflect gas exchange at the lung level (i.e., external respiration). |
|-------------------|--|

**Other parameters**

|                         |  |
|-------------------------|--|
| Heart rate (pulse rate) | The number of beats, or cardiac cycles per minute.   |
| %HRmax                  | Percentage of maximal heart rate. Maximal heart rate is commonly estimated as 220 – the age of a given individual.   |
| Dyspnea Index           | A scale indicating the subjective assessment of breathlessness by an individual (scale, 1-4). A score of 1 indicates minimal dyspnea while a score of 4 is an intolerable amount of dyspnea. |

RPE Rating of perceived exertion, a subjective assessment of the degree of exertion (scale, 6-20). Scores near six indicate resting levels of exertion while scores near 20 indicate maximal levels of exertion.

### Noteworthy terms

Obstruction A class of lung disorders characterized by trouble exhaling air. The defect in virtually-all obstructive disorders is in the airways (e.g. chronic bronchitis and asthma), or affects the airways (e.g. emphysema).

Restriction A class of lung disorders characterized by trouble inspiring air. Restrictive defects can be in the alveolar area (e.g. pneumonia, asbestosis, etc.), or chest wall (e.g. obesity, rib-cage arthritis).

WOB Work of breathing, the amount of energy consumed by the respiratory muscles. Typically, the work of breathing is indirectly measured via oxygen consumption ( $\text{VO}_2$ ) methodology, or directly measured by pressure-volume methodology, which is most accurate.

Pulmonary regarding the lungs, in this article typically refers to ventilation, ventilatory-drive, and respiration, collectively.

**Note.** *Many pulmonary parameters could be classified in more than one category (e.g. RR could be classified as a ventilation or ventilatory-drive parameter), and many pulmonary parameters are not independent of one another (e.g. %SpO<sub>2</sub> is not independent of RR for a given exercise intensity).*

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