Exercise Dose–Response of the $\dot{V_E}/\dot{VCO}_2$ Slope in Postmenopausal Women in the DREW Study

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ABSTRACT

ANAYA, S. A., T. S. CHURCH, S. N. BLAIR, J. N. MYERS, and C. P. EARNEST. Exercise Dose–Response of the $\dot{V_E}/\dot{VCO}_2$ Slope in Postmenopausal Women in the DREW Study. Med. Sci. Sports Exerc., Vol. 41, No. 5, pp. 971–976, 2009. Purpose: Being overweight/obese, having hypertension, and being postmenopausal are risk factors for the development of congestive heart failure (CHF). A characteristic of CHF is an abnormal $\dot{V_E}/\dot{VCO}_2$ slope, which is predictive of mortality in patients with CHF. Although the $\dot{V_E}/\dot{VCO}_2$ slope is well established in CHF patients, little is known regarding interventions for “at-risk” populations. Methods: We examined the $\dot{V_E}/\dot{VCO}_2$ slope in 401 sedentary, overweight, moderately hypertensive women randomized to 6 m of nonexercise (control) or 4 doses of 8 KKW or greater seems to present an adequate dose of exercise to promote small but significant reductions in the $\dot{V_E}/\dot{VCO}_2$ slope in postmenopausal women who exhibit risk factors associated with the development of CHF. Key Words: BLOOD PRESSURE, SEDENTARY, VENTILATORY EFFICIENCY, CARDIORESPIRATORY FITNESS

The incidence of cardiovascular disease and congestive heart failure (CHF) increases in women after menopause (11,20,21). Similarly, the incidence of CHF increases with elevated blood pressure (22,32). For example, statistics from the Framingham Heart Study and the American Heart Association shows that the risk of developing CHF doubles with a blood pressure >160/90 mm Hg and that 75% of CHF patients have a history of high blood pressure (22,32). In 2004, approximately 160,000 women in the United States died of CHF, and in 2005, the prevalence of CHF in women older than 20 yr rose to 2.7 million (32). Aging also plays an important role in the development of CHF. Data from the Women’s Health Initiative (WHI) Observational Study show that women in their 70s have a greater prevalence of hypertension than women in their 50s and that there is an exponential increase in the 10-yr cardiovascular incidence of CHF as blood pressure increases (19,26,34). Further, the WHI Observational Study also shows that approximately two thirds of postmenopausal women do not have their blood pressure under control (34). Clinically, this is important because the Heart and Estrogen/Progestin Replacement Study (HERS) trial reported that postmenopausal women with CAD were at a greater risk for developing CHF when systolic blood pressure was greater than 120 mm Hg and body mass index (BMI) was >35 kg m$^{-2}$ (7). Therefore, postmenopausal women who become overweight and hypertensive may be more likely to develop CHF.
It is estimated that there will be more than 1.2 billion women in the world older than 50 yr by the year 2030 (20). Many large-scale studies have demonstrated the importance of preventing and treating cardiovascular disease in postmenopausal women (7,18,27,33,34). Although many studies examining cardiorespiratory exercise attest to the benefit of higher fitness (i.e., $\dot{V}O_{2\text{max}}$), few studies have examined other physiologic changes associated with exercise training after menopause. Recently, we reported results from the DREW study showing that exercise training at 50%, 100%, and 150% of the National Institutes of Health (NIH) Consensus Development Panel on minimal physical activity recommendations improved the $\dot{V}O_{2\text{max}}$ of postmenopausal women (8). In the current report, we examine women from the DREW cohort for the effects of exercise training on the parameter known as the $\dot{V}E/\dot{V}CO_2$ slope.

The $\dot{V}E/\dot{V}CO_2$ slope is the slope of the relationship between ventilation and carbon dioxide production during exercise. During incremental exercise to exhaustion, the $\dot{V}E/\dot{V}CO_2$ slope is heightened in those with CHF compared with normal subjects. Overall, the $\dot{V}E/\dot{V}CO_2$ slope is strongly predictive of mortality and other outcomes in patients with CHF and can be measured using submaximal and maximal exercise tests (3). Yet, little is known regarding preventive interventions in at risk populations regarding this parameter (1,2,9,25,35). Although research has been conducted on postmenopausal women with CHF, and separately on the relationship between the $\dot{V}E/\dot{V}CO_2$ slope and outcomes in patients with CHF, we are unaware of any studies examining the $\dot{V}E/\dot{V}CO_2$ slope response to exercise training in postmenopausal women with elevated risk factors corresponding to the development of CHF. The aim of our current study was to evaluate the response of the $\dot{V}E/\dot{V}CO_2$ slope to different physical activity levels in postmenopausal, moderately hypertensive, and previously sedentary overweight women.

**METHODS**

We have previously published a detailed description of the DREW design, methods, and primary outcomes for the current cohort (8,24). These manuscripts detail how the sample size was derived for the main outcomes, the randomization sequence and allocation procedures, blinding techniques, recruitment, and adverse events. In brief, DREW is a randomized, dose–response, double-blind, exercise training trial that complies with Declaration of Helsinki and is composed of a nonexercise control group and three exercise training groups exercising at incremental doses (50%, 100%, and 150%) of the minimal NIH Panel’s recommendation for energy expenditure. Overall, we recruited patients via telephone screening interviews ($n = 4545$) between April 2001 and June 2005. After providing written informed consent, 464 postmenopausal women aged 45 to 75 yr who were sedentary (not exercising $\geq 20$ min on $\geq 3$ d wk$^{-1}$, and taking $< 8000$ steps per day assessed during the course of 1 wk), overweight or obese (body mass index of 25.0–43.0 kg m$^{-2}$), and had a systolic blood pressure that ranged from 120.0 to 159.9 mm Hg were randomly assigned to one of the four groups. Exclusion criteria included history of stroke, heart attack, or any serious medical condition that prevented participants from adhering to the protocol or exercising safely. Participants were recruited using a wide variety of techniques, including newspaper, radio, television, mailers, community events, and e-mail distributions.

The study was originally reviewed annually by The Cooper Institute and subsequently approved by the Pennington Biomedical Research Center’s IRB for the continued analysis. Before participation, all participants signed a written informed consent document outlining the procedures involved in the DREW study. The primary outcomes for the DREW study included peak aerobic power and resting blood pressure (8,24). The data presented herein are the result of secondary analysis examining the $\dot{V}E/\dot{V}CO_2$ slope response to our training intervention.

After an initial run-in period, we randomized 464 postmenopausal women (45–75 yr) to one of three exercise training groups or a nonexercise control for a 6-month intervention period. However, given that our current analysis was not originally considered during the initial planning of our study and was considered only after the study’s completion, we focused the $\dot{V}E/\dot{V}CO_2$ slope analysis only on those women who met the criteria for $\dot{V}O_{2\text{max}}$ (outlined below). Study participants were sedentary (exercising $< 20$ min, $< 3$ d wk$^{-1}$, $< 8000$ steps per day assessed during the course of 1 wk), overweight or obese (BMI 25.0–43.0 kg m$^{-2}$), and had a systolic blood pressure between 120.0 and 159.9 mm Hg. As previously reported, there was no difference in this cohort at baseline or after the intervention for fasting measures of cholesterol, triglycerides, and glucose (8). We excluded women who had a history of stroke, heart attack, or any serious medical condition that prevented participants from adhering to the protocol or exercising safely.

**Daily physical activity and exercise training.** To assess potential changes in nonsupervised physical activity, all randomized participants wore a step counter (Accusplit Eagle, Pleasanton, CA) to record their daily steps. Cardiovascular exercise training consisted of having women expend 4, 8, or 12 kcal kg$^{-1}$wk$^{-1}$ (KKW). During their exercise training sessions, women alternated exercise training using a recumbent cycle ergometer or treadmill. The target training intensity for each exercise training session was set at an HR corresponding to 50% of each woman’s baseline $\dot{V}O_{2\text{max}}$. A computer-controlled exercise training management system was used, which allowed the input of relevant data points on each woman (week of exercise, KKW dose according to group assignment, their training HR zone, body weight, and number of visits per week). The computer then provided the appropriate power output (PO) for the cycle ergometer and the correct speed...
and grade for the treadmill. By knowing the exact PO for the cycle ergometer and the treadmill, the total kilocalories expended each minute and the time needed to reach the target energy expenditure for the exercise session or for the week was calculated. The duration of each individual session depended on the number of visits required to reach the target KKW. To monitor the participant’s caloric expenditure during the course of 6 months, we created a weekly tracking report, which was used to track and calculate caloric adjustments. The number of calories expended per session was adjusted each week, within the limits of the study design so that the total number of calories expended was equal to the total number prescribed per week for the 24-wk program. This report also averaged the number of visits per week so that it could be determined whether the participants were exercising at least two, but no more than four, sessions each week.

During exercise, HR was monitored every 3–6 min using a Polar HR monitor (Polar Vantage XL and Polar Vantage NV, Lake Success, NY). The target HR was used to monitor each woman’s performance during each session to ensure that she was exercising at the proper intensity. Monitoring HR permitted the control of exercise intensity and documentation of the specific amount of exercise done during each session. As women improved their fitness, they worked at gradually higher PO and spent less time to expend the required KKW. We contacted anyone if they missed a scheduled session so that arrangements could be made to bring them back on schedule as soon as possible. As previously reported, the nonexercise training control group maintained their current level of activity during the trial, showed no significant increase in outside physical activity, and adhered well to their prescribed exercise training, as 92% of the exercise training sessions were completed (8).

**Fitness testing and \( \dot{V}_E/\dot{V}CO_2 \) slope assessment.** Fitness testing was conducted using a Lode Excalibur Sport cycle ergometer (Groningen, the Netherlands), an electronic, rate-independent ergometer. Participants performed two maximal exercise tests at baseline and at follow-up by cycling at 30 W for 2 min, 50 W for 4 min, followed by increases of 20 W every 2 min until they could no longer maintain a pedal cadence of 50 rpm. Each exercise test was separated by 48–72 h. Respiratory gases were measured using a Parvomedics TrueOne® 2400 Metabolic Measurement Cart (Sandy, UT). Volume and gas calibrations were conducted before each test. Gas exchange variables (\( VO_2 \), \( CO_2 \) production, ventilation, and RER) were recorded every 15 s. HR was measured directly from the ECG monitoring system. RPE values were obtained using the 20-point Borg scale. Fitness was defined as the mean of two exercise test assessments at both baseline and 6 months. The reproducibility of the two fitness tests was examined and was characterized by an intraclass correlation observed for absolute \( VO_2 \) expressed as liters per minute (0.88) and maximal HR (0.74) at both baseline and follow-up testing. To examine the \( \dot{V}_E/\dot{V}CO_2 \) slope, all expiratory gases were examined in 1-min averages. The \( \dot{V}_E/\dot{V}CO_2 \) slope was defined as the slope of the relationship between ventilation and carbon dioxide production throughout the entire exercise test, of each maximal exercise test using the equation:

\[
\dot{V}_E \left( \text{L}\cdot\text{min}^{-1} \right) = m \dot{V}CO_2 \left( \text{L}\cdot\text{min}^{-1} \right) + b,
\]

where \( m = \dot{V}_E/ \dot{V}CO_2 \) slope.

**Statistical analysis.** As previously reported, statistical power considerations for the original study design were on the basis of changes in systolic blood pressure and changes in \( VO_2\text{max} \) (8,24). These calculations assumed that 10% of participants would drop out during 6 months and that 15% of partial adherers would gain half the benefit of fully adherent exercisers. Extra participants were allotted to the 4-KKW condition to increase power for smaller anticipated fitness gains in this group. Statistical power was estimated to range from 85% to 99% for detecting fitness increases ranging from 7% to 15% tested at 5% significance and 97% for testing a linear dose–response trend across exercise levels. We anticipated reductions of 5, 7, and 9 mm Hg in systolic blood pressure at 6 months across the three increasing dose levels and a change score SD of 9 mm Hg. We computed the statistical power to be 0.84, 0.98, and 0.99 for the 4-, 8-, and 12-KKW groups, respectively, for significant reductions in systolic blood pressure compared with those in the control group. The test for a significant dose–response trend across the three exercise groups has a power of 85%. We compared the baseline characteristics between exercise groups using \( t \)-tests or chi-square tests as appropriate. To examine the \( \dot{V}_E/\dot{V}CO_2 \) slope treatment effects of the DREW intervention, we averaged the two baseline and follow-up \( \dot{V}_E/\dot{V}CO_2 \) slopes into one value. Further, we examined both the baseline and follow-up \( \dot{V}_E/\dot{V}CO_2 \) slope assessments via intraclass correlations and examined the potential dose effect for the trend of our exercise treatments by performing a linear regression using the dose of exercise compared with the change in \( \dot{V}_E/\dot{V}CO_2 \) slope. We also used a subgroup analysis to compare the dose–response effects across predefined baseline groups with significance of interactions assessed by the multiple regressions using a Spearman correlation analysis and denoted as \( r_s \). Lastly, we used a mixed linear model with covariance components to examine the influence of the different doses of exercise training on the \( \dot{V}_E/\dot{V}CO_2 \) slope. The decision to present mean or percent change data was predicated on examining the normality of the individualized residual differences between the predicted change and actual changes of the \( \dot{V}_E/\dot{V}CO_2 \) slope. Normality characteristics were determined via the Shapiro–Wilks test. We adjusted all of our outcomes among the randomization groups for the baseline \( \dot{V}_E/\dot{V}CO_2 \) slope. We further explored significant statistical effects (time and group) and
statistical interactions (time × group) using a Dunnett–Hsu post hoc assessment versus control. The Dunnett–Hsu test allows for specific multiple pairwise comparisons while still protecting against Type I statistical errors. All reported P values are two-sided (P < 0.05). All statistical analyses were performed using JMP software (Cary, NC).

RESULTS

For our primary analysis, we successfully analyzed the \( \dot{V}_E/\dot{V}CO_2 \) slope of 401 women (mean ± SD: age 57 ± 6 yr, BMI 32.1 ± 5.1 kg·m\(^{-2}\)). Study participants were sedentary (exercising <20 min, <3 d·wk\(^{-1}\), <8000 steps per d assessed during the course of 1 wk), overweight or obese (BMI 25.0–43.0 kg·m\(^{-2}\)), and had a systolic blood pressure between 120.0 and 159.9 mm Hg (Table 1). At baseline, we observed small, yet significant associations with age and absolute \( VO_2_{max} \) but not for weight, BMI, or relative \( VO_2_{max} \) compared with the \( \dot{V}_E/\dot{V}CO_2 \) slope. When expressed as change from baseline to posttest, the \( \dot{V}_E/\dot{V}CO_2 \) slope demonstrated a small but significant association with changes in absolute and relative \( VO_2 \) (Table 1). We observed an intraclass correlation of 0.68 and 0.64 for our baseline and follow-up examinations of \( \dot{V}_E/\dot{V}CO_2 \) slope, respectively.

As a result of our regression analysis, we observed a significant trend for a reduction in the \( \dot{V}_E/\dot{V}CO_2 \) slope (P < 0.004) associated with increasing energy expenditure (i.e., KKW). Specifically, the estimated regression line was \( \dot{V}_E/\dot{V}CO_2 \) slope = \(-0.29 \pm 0.12 \) KKW; thus, the predicted decrease in \( \dot{V}_E/\dot{V}CO_2 \) slope was \(-0.12 \) for every one unit change in KKW. The normality characteristics of the mean change and percent change data showed normal distribution characteristics for both analyses. On the basis of these findings, we chose to present the results of the mean change data to maintain the continuity of our presented findings with those previously reported in our primary outcomes paper (8). For our mixed linear model with covariance components analysis, we observed significant between- and within-group interactions for time, group, and the time-by-group treatment interactions (all, P < 0.002) for the \( \dot{V}_E/\dot{V}CO_2 \) slope. No post hoc differences were observed for the comparison of our mean data within each treatment group. However, for our post hoc comparisons of mean change data, we observed that both the 8- and 12-KKW groups showed a significantly greater reduction in the \( \dot{V}_E/\dot{V}CO_2 \) slope compared with the control group, whereas the 12-KKW group exhibited a greater reduction in the \( \dot{V}_E/\dot{V}CO_2 \) slope compared with the 4-KKW group (all, P < 0.05; Fig. 1).

### TABLE 1. Baseline characteristics of DREW participants.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Total Cohort (N = 401)</th>
<th>Control (n = 89)</th>
<th>4 KKW (n = 136)</th>
<th>8 KKW (n = 87)</th>
<th>12 KKW (n = 89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>57.13 (6.3)</td>
<td>57.1 (5.9)</td>
<td>57.77 (6.4)</td>
<td>56.62 (6.5)</td>
<td>56.69 (6.5)</td>
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<tr>
<td>Anthropometry, mean (SD)</td>
<td></td>
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<tr>
<td>Weight (kg)</td>
<td>84.70 (11.9)</td>
<td>86.5 (11.8)</td>
<td>83.9 (10.9)</td>
<td>85.3 (13.0)</td>
<td>83.6 (11.3)</td>
</tr>
<tr>
<td>BMI (kg·m(^{-2}))</td>
<td>32.07 (5.1)</td>
<td>32.35 (3.8)</td>
<td>32.37 (7.0)</td>
<td>32.27 (4.1)</td>
<td>31.16 (3.5)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>101.36 (11.6)</td>
<td>103.34 (12.0)</td>
<td>100.68 (11.1)</td>
<td>102.22 (11.9)</td>
<td>99.69 (11.7)</td>
</tr>
<tr>
<td>Cardiovascular, mean (SD)</td>
<td></td>
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<td></td>
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<tr>
<td>( VO_2_{max} ) (mL·kg(^{-1})·min(^{-1}))</td>
<td>1.30 (0.3)</td>
<td>1.34 (0.3)</td>
<td>1.28 (0.3)</td>
<td>1.27 (0.2)</td>
<td>1.31 (0.3)</td>
</tr>
<tr>
<td>( VO_2_{max} ) (L·min(^{-1}))</td>
<td>15.46 (2.9)</td>
<td>15.57 (3.0)</td>
<td>15.39 (3.0)</td>
<td>15.02 (3.0)</td>
<td>15.86 (3.0)</td>
</tr>
<tr>
<td>( \dot{V}_E/\dot{V}CO_2 ) slope</td>
<td>32.55 (4.7)</td>
<td>31.87 (4.4)</td>
<td>33.43 (5.0)</td>
<td>31.65 (4.4)</td>
<td>32.69 (4.8)</td>
</tr>
<tr>
<td>Blood pressure (mm Hg), mean (SD)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Systolic</td>
<td>139.36 (12.9)</td>
<td>141.18 (11.5)</td>
<td>138.46 (10.3)</td>
<td>140.23 (13.6)</td>
<td>138.12 (13.2)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>80.84 (8.6)</td>
<td>80.74 (7.9)</td>
<td>80.58 (8.9)</td>
<td>81.36 (8.5)</td>
<td>80.82 (8.8)</td>
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<tr>
<td>Medication history, n (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Antihypertensive</td>
<td>113 (27.9)</td>
<td>23 (5.7)</td>
<td>26 (6.4)</td>
<td>25 (8.6)</td>
<td>29 (7.2)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>61 (15.1)</td>
<td>15 (3.7)</td>
<td>14 (3.5)</td>
<td>14 (3.5)</td>
<td>15 (3.7)</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>73 (18.0)</td>
<td>15 (3.7)</td>
<td>24 (5.9)</td>
<td>15 (3.7)</td>
<td>19 (4.7)</td>
</tr>
<tr>
<td>Hyperlipidemic</td>
<td>64 (15.8)</td>
<td>14 (3.5)</td>
<td>27 (6.7)</td>
<td>12 (3.0)</td>
<td>11 (2.7)</td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
<td>178 (45.9)</td>
<td>45 (11.6)</td>
<td>55 (14.2)</td>
<td>36 (9.3)</td>
<td>42 (10.8)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Never</td>
<td>139 (46.0)</td>
<td>44 (11.7)</td>
<td>73 (19.3)</td>
<td>49 (13.0)</td>
<td>50 (13.2)</td>
</tr>
<tr>
<td>Past</td>
<td>140 (23.0)</td>
<td>28 (10.0)</td>
<td>52 (13.7)</td>
<td>31 (8.2)</td>
<td>42 (11.1)</td>
</tr>
<tr>
<td>Current</td>
<td>23 (7.6)</td>
<td>6 (1.9)</td>
<td>6 (2.6)</td>
<td>3 (1.0)</td>
<td>8 (2.6)</td>
</tr>
</tbody>
</table>

Statistical notations describe significant \( \dot{V}_E/\dot{V}CO_2 \) slope associations at baseline: * \( \beta \) = 0.17, P < 0.0006 and \( \beta \) = 0.11, P < 0.03, after 6 months of exercise intervention; ** \( \beta \) = 0.10; P = 0.06, *** \( \beta \) = 0.10, P = 0.05; and change between the baseline posttest exercise intervention testing \( \beta \) * \( \beta \) = 0.11, P < 0.04.

FIGURE 1—Data represent the least-squares means adjusted for baseline \( \dot{V}_E/\dot{V}CO_2 \). Error bars indicate 95% CI. P values for pairwise comparisons of control with the 4-, 8-, and 12-KKW groups. * Represents a significant difference versus control (P < 0.05). ** Represents a significant difference versus 4 KKW (P < 0.05). § Represents a significant P for trend for dose of exercise versus mean change (P < 0.004).
DISCUSSION

The primary aim of our current analysis was to examine the association between exercise training and the $\dot{V}_E/\dot{V}CO_2$ slope in overweight, sedentary, and postmenopausal women with elevated blood pressure. Unlike previous studies examining the prognostic value of the $\dot{V}_E/\dot{V}CO_2$ slope, our participants did not have CHF. Therefore, the analysis focused on exercise as a preventative step in women at increased risk for CHF. To this end, we found that the $\dot{V}_E/\dot{V}CO_2$ slope showed small, yet significant relationships to age and absolute $VO_{2\text{max}}$ at baseline. After 6 months of exercise training, the $\dot{V}_E/\dot{V}CO_2$ slope was related to mean and relative changes in $VO_{2\text{max}}$. Despite a trend for improvement in the four treatment groups, we only observed statistical significance for the mean change in the $\dot{V}_E/\dot{V}CO_2$ slope (vs control) for those exercising at 8 and 12 KKW (Fig. 1). These findings suggest that improvements in the $\dot{V}_E/\dot{V}CO_2$ slope are dose-dependent relative to total energy expenditure in a population who is at risk for CHF.

Currently, there are no normal standards for the expression of the $\dot{V}_E/\dot{V}CO_2$ slope. Some investigators have theorized that it is better to use data from the entire test, whereas still others suggest the exclusion of those data points beyond the ventilatory threshold when calculating the $\dot{V}_E/\dot{V}CO_2$ slope (5). However, a recurring metric from the literature is that a $\dot{V}_E/\dot{V}CO_2$ slope greater than 34 or 35 is predictive of future cardiac events (12,15) and an increased risk of mortality occurs with an increasing slope (4,16). Reindl and Kleber (30) also found that the $\dot{V}_E/\dot{V}CO_2$ slope correlated with the severity of heart failure as defined by the New York Heart Association’s classification. Interestingly, ~27% of our population presented with a $\dot{V}_E/\dot{V}CO_2$ slope $\geq$35, a value associated with higher risk among patients with CHF (12,14,15,25). Further, our participants presented with a low functional capacity, with values that are slightly above heart transplantation criteria (i.e., <14 mL·kg$^{-1}$·min$^{-1}$, probable indication; <10 mL·kg$^{-1}$·min$^{-1}$, acceptable indication) as defined by the American College of Cardiology/American Heart Association (2,13). Although we do not wish to imply that women in the DREW cohort are candidates for heart transplantation, it is noteworthy that the low functional capacity and relatively high $\dot{V}_E/\dot{V}CO_2$ slope in these women place them near the upper limit of several well-defined risk factors associated with a higher risk for developing CHF.

Overall, the mechanisms underlying an increased $\dot{V}_E/\dot{V}CO_2$ slope include an excess physiologic dead space (30,31), excess dead space due to an unknown underlying cause (9), ventilation-to-perfusion mismatch (6), early blood lactate accumulation, and ergoreflex activation (28,30). Moreover, most studies examining the prognostic value of the $\dot{V}_E/\dot{V}CO_2$ slope have been performed in male patients with CHF. A primary strength of the DREW study is that it is a population at risk for developing cardiovascular disease due to elevated blood pressure, age, and a sedentary lifestyle. When coupled with the low functional capacity of this cohort, the women in the DREW share similar characteristics to those diagnosed with CHF. Although we did not measure the mechanisms of action outlined above, our results agree with various studies in CHF patients showing an inverse association with maximal aerobic capacity and the $\dot{V}_E/\dot{V}CO_2$ slope associated with exercise. For example, improvements in the $\dot{V}_E/\dot{V}CO_2$ slope among males have been demonstrated in several randomized trials (9,10,17,30).

To our knowledge, the DREW study is the first to examine the $\dot{V}_E/\dot{V}CO_2$ slope relative to a specific dose of aerobic exercise. A potential criticism of our paper is that we used cycle ergometry rather than treadmill testing to determine maximal aerobic capacity. As such, some reports suggest that cycle ergometry produces ~10%-20% lower measures of maximal aerobic capacity than treadmill testing (23,29). Even considering the variance associated with treadmill testing, the $VO_{2\text{max}}$ values in the current cohort would still be similar to those with diminished functional capacity and/or CHF. However, our participants had similar $\dot{V}_E/\dot{V}CO_2$ slope values, which are predicated on the relationship between ventilation and the associated $CO_2$ production throughout rather than at peak exercise.

A major strength of the DREW study is that it was an efficacy study, using a tightly controlled exercise dose, with extensive monitoring of exercise energy expenditure, HR, and steps taken outside the structured exercise prescription. With the efficacy of the exercise dose–response demonstrated in DREW, it will be feasible to conduct effectiveness studies to evaluate the extent to which the findings can be generalized. Our findings suggest a significant dose-dependent trend for improvement in the $\dot{V}_E/\dot{V}CO_2$ slope with increasing weekly exercise energy expenditure. Although our data in this study examining mean slope change became significant at an exercise dose of 8 and 12 KKW, it would be unreasonable to suggest that lesser doses of exercise offer no value for improvement.

CONCLUSIONS

Despite the observation that the DREW cohort seemed generally healthy, the presence of a relatively low baseline $VO_{2\text{max}}$ and elevated $\dot{V}_E/\dot{V}CO_2$ slope values suggest that these women approach levels similar to those observed in patients with CHF. The results of our current analysis indicate a dose–response improvement in $\dot{V}_E/\dot{V}CO_2$ with increasing levels of energy expenditure at moderate-intensity exercise levels. Specifically, moderate-intensity exercise at 8 KKW or greater seems to present an adequate dose of exercise to promote small but significant reductions in the $\dot{V}_E/\dot{V}CO_2$ slope in postmenopausal women who exhibit risk factors associated with the development of CHF.

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REFERENCES

8. Church TS, Earnest CP, Skinner JS, Blair SN. Effects of different doses of physical activity on cardiorespiratory fitness among sedentary, overweight or obese postmenopausal women with elevated blood pressure: a randomized controlled trial. JAMA. 2007;297:2081–91.