Short-term aerobic training and circulatory function in women: age and hormone-replacement therapy

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ABSTRACT

The physiological basis of training responses in women, and particularly older women, is not well understood. Short-term aerobic training (STAT) was used to probe the effects of age and hormone-replacement therapy (HRT) on women’s ability to rapidly change peak uptake ($\dot{V}_\text{O}_2\text{max}$), plasma volume and cardiac function. A total of 39 females participated in the STAT programme: 15 younger (Y; aged 19–29 years), 12 postmenopausal women undergoing HRT and 12 non-medicating postmenopausal (PM) women (aged 60–75 years). Training consisted of ten sessions of cycling over a 2-week period, which progressed in duration from 20 to 60 min and in intensity from 60–75% of maximum heart rate. Plasma volume (PV; as determined by Evan’s Blue dye dilution), $\dot{V}_\text{O}_2\text{max}$ (cycle ergometry) and cardiac function (radionuclide ventriculography) were analysed using analysis of covariance or repeated measures ANOVA. All groups demonstrated similar increase in $\dot{V}_\text{O}_2\text{max}$ (Y, 13%; PM, 17%; HRT, 13%), but without a significant change in left-ventricular ejection fraction and diastolic function or volumes during supine exercise. PV expansion was observed among the Y group (7%; $P < 0.05$) but not the PM group (2%; $P > 0.05$) or women undergoing HRT (1%; $P > 0.05$). Age and hormone-replacement status did not affect the magnitude of $\dot{V}_\text{O}_2\text{max}$ change. This study suggests that STAT improves $\dot{V}_\text{O}_2\text{max}$, independent of central adaptations.

INTRODUCTION

Although it was once viewed only as a health risk of middle-aged men, cardiovascular disease is now recognized as a leading cause of death in women. Mortality due to heart disease increases sharply after the menopause and, for women aged 70–75 years, exceeds that of surviving age-matched males. An inverse relationship between fitness level and heart disease risk factors, including blood pressure (BP), body fat and blood lipid profile, has been established for older women. Rehabilitation programmes targeted at older women have been initiated, yet little is known of gender-specific mechanisms of exercise conditioning.

Training studies have traditionally utilized male study groups. Recent studies of older men and postmenopausal women suggest that cardiovascular adaptations, including an increase in ejection fraction, end diastolic volume and cardiac output occur selectively in older males [1–3]. Training-induced increases in end diastolic volume and cardiac output are in part mediated by increases in plasma volume (PV) [4–6].

Key words: aging, blood volume, gender, hormone replacement status, stroke volume.
Abbreviations: ANCOVA, analysis of covariance; $a-\dot{V}_\text{O}_2\text{(diff)}$, difference between arterial and mixed venous oxygen content; BP, blood pressure; BV, blood volume; HRT, hormone-replacement therapy; PV, plasma volume; STAT, short-term aerobic training; $\dot{V}_\text{O}_2\text{max}$, peak oxygen uptake.
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PV expansion can result from high-intensity training durations, ranging from 2 to 10 days in young males and females \([4,7,8]\). Petrella et al. \([9]\) observed that 5 days of training in older males resulted in a 6% increase in PV that correlated to improved cardiac filling. Equivalent short-duration programmes among older female subjects have not been reported. A study that utilized a 12-week programme indicated that aerobic capacity is improved in postmenopausal women without a change in PV \([10]\).

Long-term training studies with older women suggest that increases in peak oxygen uptake \((\dot{V}_{O_2\text{max}})\) are not mediated by improvements in left-ventricular performance \([3]\) or physiological ventricular hypertrophy \([2]\).

Several authors have suggested that gender differences in training responses may be due, in part, to oestrogen deficiency associated with menopause \([1–3]\); however, the role of oestrogen in determining response to training remains unclear since, whereas some studies have evaluated the effect of oestrogen \([11]\), others have evaluated training responses \([2,3]\), but few \([12]\) have examined the effect of training with and without long-term oestrogen hormone-replacement therapy (HRT).

Studies have demonstrated that a 2-week training duration is sufficient to increase \(\dot{V}_{O_2\text{max}}\), PV and cardiac function in males, but there are no equivalent studies of the response to short-term aerobic training (STAT) in women. The objectives of this study were therefore to compare the central training adaptations to a 2-week STAT programme in young and older, postmenopausal female subjects. The effect of long-term (more than 2 years) HRT was examined cross-sectionally by comparing older women without HRT with those receiving HRT. We hypothesized that STAT would increase PV, cardiac function and \(\dot{V}_{O_2\text{max}}\), and that the magnitude of change will be greatest in younger females, and least for older women not taking HRT.

**METHODS**

A total of 39 healthy, but physically inactive, women were recruited to participate in the study: 15 younger women (mean age 26±1.1 years), 12 older women who were not undergoing HRT (67.5±1.5 years), and 12 older women (63.2±1.0 years) who were undergoing combined HRT. The HRT subjects were taking cyclic Premarin® and Provera® for 8.2±3.3 years (see Table 1).

Recruitment was conducted through advertisements in local newspapers, hospitals, as well as from physician referral from the Women’s Cardiovascular Health Initiative programme at Sunnybrook Women’s College Health Science Center, Toronto, ON, Canada. Written informed consent, as approved by the University of Toronto Human Ethics Committee, was obtained after a full explanation of purpose, methods, risks and benefits of the study. All women were not taking medication, with the exception of the HRT group, were non-smokers, and were without evidence of disease or orthopaedic dysfunction that would preclude participation in a cycle ergometer programme. Regular physical activity did not exceed 1 h per week. Prior to enrolment, a medical history and measurements of BP, heart rate, and resting ECG were recorded. \(\dot{V}_{O_2\text{max}}\), PV and radionuclide left-ventricular function measures were taken over three visits before and after training. Younger women were tested the week following menses (follicular phase), both before and after training, by starting training 2 weeks after the initial measurement.

**Exercise tests**

\(\dot{V}_{O_2\text{max}}\) was evaluated in a climate-controlled exercise laboratory using a supervised graded cycle ergometer (Monark Model 818) exercise test. Prior to each test, resting BP (manual sphygmomanometer) and 3-lead ECG (Burdick EK 10) were measured, and subjects were oriented regarding the purpose of testing, cycle resistance levels, cadence and the modified Borg Scale of exertion. After a 2-min warm-up at 29.4 W, the power output was increased by 14.7 W every 30 or 60 s for younger and older patients respectively until exhaustion. BP, ratings of perceived exertion, and ECG were recorded every 60 s. \(\dot{V}_{O_2\text{max}}\) was determined using open circuit spirometry (Airspec 3000) with on-line breath-by-breath calculation of alveolar gas exchange. Exercise was stopped at the subject’s request or (i) when BP exceeded 200/110 mmHg, (ii) when oxygen consumption plateaued or (iii) when the subject was unable to maintain cadence of at least 60 rev./min with increasing load.

**Vascular volumes**

Subjects were instructed to abstain from caffeine for 24 h before testing and to maintain a high sodium intake. After an overnight fast \([1]\), PV determinations were made with the subjects in the supine position. An intravenous catheter (Becton Dickinson Insyte 18-G), inserted in the antecubital vein, was attached to a three-way stopcock.

**Table 1** Group differences in subject characteristics at baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Younger (n = 15)</th>
<th>Older non-HRT (n = 12)</th>
<th>Older + HRT (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>26.0±5.1†</td>
<td>67.5±1.5</td>
<td>63.2±1.0‡</td>
</tr>
<tr>
<td>Body mass (kg)</td>
<td>64.1±2.8</td>
<td>74.3±2.8</td>
<td>69.6±3.0†</td>
</tr>
<tr>
<td>Body-mass index (kg · m⁻²)</td>
<td>23.2±0.9†</td>
<td>28.5±1.1</td>
<td>27.0±1.3</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>110±2*†</td>
<td>136±4</td>
<td>131±3</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>74±1*†</td>
<td>88±2</td>
<td>84±2</td>
</tr>
<tr>
<td>PV (ml/kg)</td>
<td>47.8±2.5*</td>
<td>39.2±2.0</td>
<td>42.2±1.8</td>
</tr>
<tr>
<td>Duration of HRT (years)</td>
<td>NA</td>
<td>NA</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Values are means ± S.E.M. NA, not applicable. *P < 0.05 compared with the non-HRT group; †P < 0.05 compared with the HRT group.
Table 2  Maximal exercise and haematological measures before and after STAT for younger women, older women and older women receiving HRT

All groups demonstrated significant (\(P < 0.05\)) increases in maximal exercise capacity, but only the younger women showed altered haematology with STAT. The significant differences are as follows: *younger women differed from the older group receiving HRT; †younger women differed from the older women; ‡change with training relative to baseline. Values are means ± S.E.M.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Young Pre</th>
<th>Young Post</th>
<th>Older Pre</th>
<th>Older Post</th>
<th>Older-HRT Pre</th>
<th>Older-HRT Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum heart rate (beats/mim)</td>
<td>178 ± 2‡</td>
<td>181 ± 2‡</td>
<td>148 ± 3</td>
<td>152.0 ± 3</td>
<td>147 ± 3</td>
<td>152 ± 3</td>
</tr>
<tr>
<td>Peak power output (W)</td>
<td>152 ± 6†</td>
<td>168 ± 6†</td>
<td>109 ± 8</td>
<td>130 ± 7†</td>
<td>111 ± 4</td>
<td>128 ± 4†</td>
</tr>
<tr>
<td>Peak respiratory exchange ratio</td>
<td>1.10 ± 0.2</td>
<td>1.10 ± 0.2</td>
<td>1.09 ± 0.25</td>
<td>1.09 ± 0.3</td>
<td>1.08 ± 0.2</td>
<td>1.07 ± 0.3</td>
</tr>
<tr>
<td>Relative PV (ml/kg)</td>
<td>47 ± 2.4†</td>
<td>51.2 ± 2.1†</td>
<td>39.2 ± 1.9</td>
<td>39.7 ± 2.0</td>
<td>42.2 ± 1.78</td>
<td>41.7 ± 1.9†</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>36.5 ± 0.5</td>
<td>36.1 ± 0.8</td>
<td>39.5 ± 0.5</td>
<td>39.7 ± 0.88</td>
<td>37.5 ± 0.8</td>
<td>37.3 ± 0.7</td>
</tr>
<tr>
<td>Haemoglobin (g/l)</td>
<td>120.1 ± 1.4</td>
<td>120.9 ± 1.8</td>
<td>132.4 ± 1.9</td>
<td>131.1 ± 2.8</td>
<td>126.0 ± 2.3</td>
<td>124.8 ± 2.5</td>
</tr>
<tr>
<td>BV (ml)</td>
<td>4379 ± 141</td>
<td>4778 ± 160</td>
<td>4458 ± 192</td>
<td>4557 ± 138</td>
<td>4127 ± 115</td>
<td>4164 ± 116</td>
</tr>
<tr>
<td>Relative BV (ml/kg)</td>
<td>69.9 ± 4.4†</td>
<td>76.6 ± 3.9†</td>
<td>59.9 ± 2.7</td>
<td>60.5 ± 2.6</td>
<td>61.4 ± 2.7</td>
<td>61.5 ± 2.6</td>
</tr>
<tr>
<td>Total blood haemoglobin (g)</td>
<td>531 ± 22</td>
<td>572.2 ± 23.0‡</td>
<td>591.1 ± 26.0</td>
<td>601.2 ± 23.7</td>
<td>516.6 ± 19.25</td>
<td>514.4 ± 18.6</td>
</tr>
</tbody>
</table>

Adaptations to short-term aerobic training

port. Plasma optical density was measured before and after injection of albumin-bound T-1824 (Evan’s Blue) solution using a modified version of the method of Chien et al. [13]. Analysis of blood samples was carried out immediately after testing. Samples were centrifuged for 30 min at 2150 g (Beckman Model TJ-6 centrifuge) and plasma absorbance was read at 610 nm (Pharmacia Biotech NovaSpec Two) [14].

Haematocrit and haemoglobin values were determined using the microcapillary tube and cyanomethaemoglobin methods respectively. The haematocrit was used for determining blood volume (BV) with a correction for trapped plasma and whole body haematocrit by multiplication by 0.96 and 0.91 respectively.

\[ BV = \frac{PV}{100/(100 - 0.8736 \times Hct)} \]

where Hct is the venous haematocrit.

The error of measurement with this technique has been reported at 2.1% in young men and women [8]. In our laboratory, variances of 2–3% are observed with repeated measures of PV.

Left ventricular function

Exercise radionuclide ventriculography was performed on different days both before and after the training. Modified in vitro red-blood-cell labelling with 30 mCi of Tc-99m took place 30 min prior to exercise [15]. Gated blood-pool images were obtained in the supine position using a standard gamma camera (Elscint Apex 409) with a 1-inch parallel hole collimator. All scintigraphic data were acquired in the left anterior oblique position with an SP-1 minicomputer 64 × 64-pixel matrix with 24 frames per cardiac cycle. Exercise began at 32.7 W and was increased by 32.7 W every 3 min as tolerated [15]. Left ventricular counts, ECG and BP data were collected at rest and during the last 2 min of each exercise level. All data were acquired in the left anterior oblique position with 24 frames per cardiac cycle. Left ventricular regions of interest were automatically determined for each frame and the time activity curve generated. The ejection fraction and peak filling rate were determined from the time–activity curve and the first derivative. Diastolic and systolic volumes were derived based on count determination from blood samples prior to and following testing.

Training programme

A 10-day programme of cycle ergometer training was initiated following baseline measurements. A moderate-intensity programme was chosen to provide an effective training stimulus while also being feasible for older women to complete. The same progression of training duration and intensity was followed by all study participants. Each session began with a 2–3-min unloaded warm-up, followed by 20 min of cycling (which progressed to 60 min), at intensities that progressed from 60% to 75% of maximal heart rate over the ten training sessions. Heart rate (Polar Sport PE 3000) and modified Borg ratings were recorded regularly.

Statistical analysis

A mixed design with cross-sectional and longitudinal comparisons was utilized to compare and contrast cardiovascular and PV responses to STAT. PV and \(V_{O2\text{max}}\) measures were analysed using analysis of covariance (ANCOVA) controlling for baseline differences between groups. Tukey comparisons were used for any between group comparisons. Measures of cardiovascular function were assessed between groups using a three-way repeated measures ANOVA, with repeated measures on time and exercise level. Wilk’s Lambda was used for testing interactions between groups for main
effects. Values are expressed as mean ± S.E.M. All statistical comparisons were made with the statistical package SAS (SAS Institute Inc., Cary, NC, U.S.A.).

RESULTS

Baseline measures of the three groups are as shown in Table 1. The younger-female group had a significantly higher baseline $V_{\text{O}_2\text{max}}$, maximum heart rate, peak ejection fraction, and lower systolic and diastolic BPs. The HRT group was generally younger, weighed less, had a lower body-mass index, and had higher measures of PV and $V_{\text{O}_2\text{max}}$ compared with the non-medicated older subjects; however, statistical analysis identified that only age and weight were significantly different. Training logs were recorded during each exercise session. Three older subjects (one HRT and two non-HRT) required an extra day of non-training due to coccyx and knee discomfort.

Maximal oxygen uptake

Results of graded cycle ergometry tests pre- and post-training are shown in Table 2. An ANCOVA controlling for baseline $V_{\text{O}_2\text{max}}$ scores found significant gains post-training without inter-group differences ($P = 0.21$). Parallel aerobic capacity improvements among groups, shown in Table 2 and Figure 1, were 13%, 17% and 15% for the young, older non-HRT and older HRT groups respectively.

Gains in aerobic power were confirmed by significantly elevated peak work rates post-training. The maximum heart rates during $V_{\text{O}_2\text{max}}$ testing were similar pre- and post-training and suggested that increased effort was unlikely to account for changed scores.

PV

The baseline PV, standardized to body mass, was similar among young and older HRT groups ($P = 0.152$), but significantly lower among older females who were not undergoing HRT ($P = 0.019$) (Table 2). After training, as shown in Table 2, only the younger group made
significant increases (7.2%) in PV (Figure 1B); however, this trend was only weakly correlated with increased aerobic capacity in the younger group.

**Radionuclide imaging measures**

The changes in left-ventricular volume, peak filling rate and ejection fraction were similar in each group, with no interaction for training effects both at submaximal and maximal exercise levels. There was a trend toward a significant interaction between training and group for heart rate (P=0.053). Left-ventricular function, represented by ejection fraction as a function of mean arterial BP [18] was unchanged at rest or peak exercise among all groups (Figures 2A–2C). No alteration in cardiac inotrophy was observed, since there was no decrease in left-ventricular end-systolic volume for a given systolic BP [18], in any of the groups from rest to peak exercise (Figure 3).

**DISCUSSION**

In this study, three groups of women trained five times per week over 10 days at intensities within the range of 60–75% of maximum heart rate. We observed that a short-duration, moderate-intensity training programme increases aerobic capacity among older and younger women, and short-duration training (10 days) results in PV expansion as a primary haematological alteration among young women. The majority (92%) of the study group complied perfectly with the prescribed programme, with the exception of three older women who required an extra non-training day owing to knee and coccyx discomfort. Our primary findings were 7% and 9% increases in PV and BV respectively among younger women only, but parallel increases in aerobic capacity among the three study groups. HRT was not an independent determinant of training adaptation for any study measures.

Moderate increases in $\dot{V}_O_{2 \text{max}}$ (4–12%) following short- and intermediate-duration programmes have been shown in younger [16] and older [9,17] men. We have demonstrated that 10 days of STAT results in parallel increases in aerobic capacity of 13%, 17% and 15% among young women, older non-HRT women and older HRT women respectively. Similar aerobic capacity increases among younger and older men have been observed with short duration [9,16] and longer duration (3–9 months) programmes [18,19]. To our knowledge, this is the first investigation that demonstrates parallel changes in younger and older women after STAT.

Training-induced hypervolaemia is induced rapidly after endurance training [4]. Short-duration, high-intensity (80–90% $\dot{V}_O_{2 \text{max}}$) programmes have yielded similar increases in PV among young [7] and older men [9]. In the present study, a 10-day programme resulted in 7% and 9% increases in PV and BV respectively among younger women. The average PV expansion (281 ml) that we observed was higher than the 186-ml expansion observed by Mier et al. [8] among younger women following 10 days of high-intensity (80–90% of maximum heart rate) training, but less than increases (15–20%) that were obtained from short-duration (2–10 days), high-intensity programmes among young men [7]. PV expansion did not occur among older women, independent of hormonal supplementation.

Cross-sectional studies report increased PV in fit women [20], while longitudinal studies report no change with training. Stachenfeld et al. [10] found no change in plasma-protein content or reduction in baroreceptor sensitivity, two factors that have been shown to favour PV expansion [4], after 12 weeks of training (65–75% of maximum heart rate) in postmenopausal women. Increased vascular volumes among older women are associated with very high levels of fitness; for example, the average $\dot{V}_O_{2 \text{max}}$ (42 ml/kg) of subjects studied by Wiebe et al. [20] was approx. double that of the post-training values that were presented by Stachenfeld et al. [10] and observed in the present study.

Krip et al. [6] demonstrated that central cardiovascular training responses are mediated, in part, by changes in vascular volumes and content. They noted that differences in maximal diastolic filling rate, stroke volume, cardiac output and total peripheral resistance between trained and untrained men were removed after respective PV reduction and expansion. High correlations among resting shortening velocity, ejection fraction, and BV adaptation were observed with a mixed sample of older women and men (six women, four men) following 16 weeks of training [21]. Short-duration training programmes minimize the likelihood of changes in intrinsic myocardial structure or function, thus suggesting a direct role of hypervolaemia in determining cardiac function [7].
Contrary to previous studies among younger and older men [3,22], we found no alteration in ventricular volumes, ejection fraction and diastolic filling rates during supine exercise in response to short-term training in either younger or older women. In young women, 10 days of high-intensity (80% of maximum heart rate) training did not increase their stroke volume response to \(\beta\)-blockade post-training [8]. Cunningham et al. [23] found neither continuous nor interval training at high intensity (80–85% of \(V_{O_{2\text{max}}}\)) elicited changes in upright stroke volume.

Examination of the relationship between systolic BP and end-systolic volume revealed no change in myocardial contractility (Figure 3); this may be related to the brief duration of the training programme. Ray et al. [22] trained young males for 8 weeks without any change in the systolic BP/end-systolic volume index. Petrella et al. [9] also found no change in contractility (fractional shortening velocity) following 5 days of training among older men; however, a significant leftward shift in the systolic BP/end-systolic volume curve during supine ergometer exercise occurred among older men following 9 months of training [18].

Findings from this study suggest cardiovascular responses to STAT among older women are similar to previous long-term training studies; increases in \(V_{O_{2\text{max}}}\) are due primarily to enhanced \(\Delta V_{O_{2\text{diff}}}\) (the difference between arterial and mixed venous oxygen content) rather than central adaptations in older women [2,3]. A mixed-gender sample of older adults studied by Seals et al. [24] increased \(V_{O_{2\text{max}}}\) primarily by increases in \(\Delta V_{O_{2\text{diff}}}\) with unchanged stroke volume, cardiac output and heart rate after 6 months of low- or high-intensity training. Moreover, Spina et al. [2] failed to find increases in stroke volume or ejection fraction in response to 9–12 months of training among postmenopausal women. In contrast, an identical training programme elicited increases in radionuclide determined ejection fraction and end-diastolic volume measures among the 60–70-year-old males studied by Ehsani et al. [18]. Spina et al. [2] suggest that the absence of increases in maximal cardiac output and stroke volume in older women following training were due to oestrogen deficiency associated with the menopause.

In summary, this study examined responses to STAT among younger and postmenopausal women. In response to the short-term, moderate-intensity programme, parallel increases in \(V_{O_{2\text{max}}}\) occurred, but training-induced hypervolaemia occurred selectively among younger women; however, training-induced hypervolaemia was only weakly associated with improvements in aerobic capacity (\(P = 0.09\)) and did not confer greater cardiovascular adaptations relative to the older groups. As suggested by Cunningham et al. [23], the significance of cardiac adaptations among young women may differ from that established in male populations. Our findings indicate that absence of cardiac training adaptations were not related to postmenopausal oestrogen deficiency.
HRT among older women conferred no greater benefits in training-induced increases in $\dot{V}O_{2\text{max}}$ or PV among older women.

The lack of improvement in indices of systolic and diastolic ventricular performance suggest, as in longer-term training programmes, that improvements in aerobic fitness may be due to altered peripheral vascular and cellular mechanisms, rather than central cardiovascular adaptation. Delineation of the optimal training pattern to enhance aerobic, functional or cardiovascular performance and the contribution of central versus peripheral mechanisms among the older women warrants future investigation.

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