Menopause, estrogen, and training effects on exercise hemodynamics: the HERITAGE study

JOHN S. GREEN, PHILIP R. STANFORTH, JACQUES GAGNON, ARTHUR S. LEON, D. C. RAO, JAMES S. SKINNER, CLAUDE BOUCHARD, TUOMO RANKINEN, and JACK H. WILMORE

Department of Health and Kinesiology, Texas A&M University, College Station, TX; Laboratory of Molecular Endocrinology, CHUL Research Center, and Physical Activity Sciences Laboratory, Laval University, Quebec City, Canada; School of Kinesiology and Leisure Studies, University of Minnesota, Minneapolis, MN; Division of Biostatistics, Washington University School of Medicine, St. Louis, MO; Department of Kinesiology, Indiana University, Bloomington, IN; and Pennington Biomedical Research Center, Baton Rouge, LA

ABSTRACT

GREEN, J. S., P. R. STANFORTH, J. GAGNON, A. S. LEON, D. C. RAO, J. S. SKINNER, C. BOUCHARD, T. RANKINEN, and J. H. WILMORE. Menopause, estrogen, and training effects on exercise hemodynamics: the HERITAGE study. *Med. Sci. Sports Exerc.*, Vol. 34, No. 1, 2002, pp. 74–82. **Purpose:** To investigate the influences of menopause, hormone replacement, and endurance exercise training on cardiovascular hemodynamics and oxygen uptake parameters during exercise in women. **Methods:** Subjects were 338 premenopausal women, 29 postmenopausal women taking hormone replacement, and 28 postmenopausal women not taking hormone replacement, all enrolled in the HERITAGE Family Study. Hemodynamic and oxygen uptake data were gathered on a cycle ergometer at 50 watts (W), 60% peak oxygen uptake, and at peak exercise, both before and after a 20-wk regimen of endurance exercise training on a cycle ergometer. **Results:** Systolic blood pressure (SBP) during peak exercise was found to be an average of 14 mm Hg less in postmenopausal women receiving hormones than in those not receiving hormones. Furthermore, menopause was associated with a 26.2 mm Hg higher SBP at 50 W power output, which remained physiologically significant after adjustment for age. At 50 W, postmenopausal women not taking hormones showed a 13.8 mm Hg greater training-induced reduction in SBP than those taking hormones. **Conclusion:** It was concluded that hormone replacement may be associated with a vasodilatory reserve at high exercise intensities and that endurance exercise training elicits favorable hemodynamic and oxygen uptake adaptations during exercise that are, in most instances, independent of menstrual status or hormone replacement. **Key Words:** MENOPAUSE, HEMODYNAMICS, ESTROGEN REPLACEMENT

The influence of hormone replacement on cardiovascular hemodynamics during exercise in postmenopausal women has not been well investigated, and the results of the few studies that exist show no consensus. More importantly, there are few dependent measures common to all studies, making comparison among studies difficult. Some studies report values assessed during maximal exercise, whereas others report submaximal values. For example, as a result of taking hormone replacement, Tankersley and et al. (26) found reduced heart rates and increased arm blood flows during submaximal exercise. No measurements of central blood flow dynamics were mentioned and no assessments during maximal exercise were made. On the other hand, Green and colleagues (5) found hormone replacement to be associated with a higher cardiac index and a lower peripheral resistance during maximal exercise, but were not able to report any values for submaximal exercise intensities. Clearly, there is a need for large cohort studies in this area that report all possible parameters pertinent to cardiovascular hemodynamics and associated oxygen uptake ($\dot{V}O_2$) parameters.

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In addition to the paucity of information concerning hormone replacement and exercise hemodynamics, there are also only a limited number of studies that address the age-controlled influence of menopause on changes in exercise hemodynamics consequent to training. Furthermore, none of these studies present complete hemodynamic profiles. Thus, the purpose of this inquiry was to explore data from female subjects in the HERITAGE Family Study in an effort to test the hypothesis that menopause and hormone replacement influence exercise hemodynamics and associated oxygen uptake parameters, both before and during endurance exercise training. The HERITAGE Family Study is a large multicenter clinical study exploring possible genetic influences on physiological response variability and the changes in risk factors for coronary disease and diabetes consequent to a regimen of endurance exercise.

METHODS

Subjects

HERITAGE subjects are from families that include natural parents and their offspring ages 17 yr and older. Subject recruitment was undertaken by each of the four clinical centers which, at the time of study onset, were located at Arizona State University, Laval University, the University

TABLE 1. Physical characteristics of the participants.[a]

Participants	Age (yr)	Height (cm)	Weight (kg)	Estradiol ($pmol \cdot L^{-1}$)	Progesterone ($nmol \cdot L^{-1}$)
All participants ($N = 395$)	33.9 ± 12.9	163.1 ± 6.5	70.5 ± 16.2	136.6 ± 171.8	1.5 ± 0.8
Premenopausal ($N = 338$)	31.0 ± 10.7	163.3 ± 6.4	70.2 ± 16.4	131.2 ± 148.2	1.5 ± 0.8
Postmenopausal ($N = 57$)	54.8 ± 5.8	161.8 ± 7.3	73.8 ± 14.6	171.6 ± 284.0	0.8 ± 0.6
No hormone ($N = 29$)	52.3 ± 6.2	162.1 ± 6.9	75.6 ± 14.0	41.3 ± 51.4	0.9 ± 0.7
Hormone ($N = 28$)	57.2 ± 4.3	161.5 ± 7.9	72.2 ± 15.3	306.8 ± 357.1	0.7 ± 0.5

[a] Data are expressed as mean ± SD.

of Minnesota, and the University of Texas at Austin. All subjects had to pass a comprehensive physical exam by a physician that included both resting and exercise electrocardiograms. The study protocol was approved by the institutional review board at each of the clinical centers and written informed consent was obtained from each subject. The subset of subjects, whose age ranged from 17 to 65 yr, included both Caucasian and African-American women. Three hundred thirty-eight were premenopausal and 57 were postmenopausal. The postmenopausal women were further subdivided into those taking ($N = 29$) and those not taking hormone replacement ($N = 28$). The postmenopausal women taking hormones had been doing so for a mean of 3.87 yr, with all subjects having taken them for a minimum of 1 yr. Although the specific drug type and dosage of estrogen and progesterone were not recorded, baseline serum levels were obtained at study onset. The means of these steroids, along with other relevant subject characteristics, are presented in Table 1.

Testing and Training Methodology

All subjects completed numerous assessments before beginning the endurance training regimen including a maximal graded exercise test, a submaximal exercise test, and a test that combined the submaximal and maximal protocols. A minimum of at least 2 d transpired between each of the three tests.

Initial maximal exercise test. The initial maximal test began at a power output of 50 watts (W) for 3 min. The rate of work was then increased in increments of 25 W every 2 min until subjects could no longer continue. For smaller or less fit individuals, the first test protocol was started at 40 W with 10- to 20-W progression increments. The results from the initial maximal test were used to calculate the power output necessary to elicit 60% of peak oxygen uptake ($\dot{V}O_{2peak}$).

Submaximal exercise test. The submaximal exercise protocol began at 50 W, which was maintained for 15 min. After a seated 4-min rest period, the subject exercised at 60% $\dot{V}O_{2peak}$ for the same time interval.

Combined submaximal and maximal test. The last of the three exercise protocols began with subjects exercising at 50 W for 15 min then continuing at 60% $\dot{V}O_{2peak}$ for 15 min. Following the completion of these first two stages, the workload was increased by 25 W every 2 min until subjects could no longer continue.

Assessments made during the tests. All three exercise tests were conducted using a SensorMedics 2900 metabolic measurement cart in conjunction with a SensorMedics Ergo-Metrics 800S cycle ergometer (SensorMedics, Yoma Linda, CA). Cycle ergometry was chosen as the exercise modality in order to facilitate more accurate blood pressure assessments and easier blood draws during exercise than could be afforded by the treadmill. $\dot{V}O_2$, carbon dioxide production, and minute ventilation were assessed every 20 s and recorded as a rolling average of the three most recent 20-s values. Criteria for the attainment of peak $\dot{V}O_2$ required the subjects to achieve one of the following: an RER > 1.1, a plateau in $\dot{V}O_2$ despite an increasing power output, or the attainment of a maximum heart rate (HR) that was within 10 beats of an age-predicted maximum. The results confirmed that mean RER for both pre- and postmenopausal women was 1.17, with the lowest value recorded being 0.97. This suggests that a true maximal effort was given by the subjects during testing. However, since cycle ergometry was used to ascertain maximal exercise parameters instead of a treadmill, a true $\dot{V}O_{2max}$ may not have been obtained. Therefore, $\dot{V}O_2$ at maximal exercise will be termed $\dot{V}O_{2peak}$. RER data at maximal exercise for all subject groupings is presented in Table 2.

Cardiac output ($\dot{Q}$)was determined using a modified Collier CO_2 rebreathing technique (29). The same electronic gas mixing system was used by all data collection centers to ensure proper CO_2 volume and concentration. HR was recorded during the last 15 s of each stage of the three protocols using electrocardiography, and systolic blood pressure (SBP) and diastolic blood pressure (DBP) were assessed using a Colin STBP-780 (San Antonio, TX) automated blood pressure unit. Stroke volume (SV) was calculated as the quotient of $\dot{Q}$ and HR, and arteriovenous oxygen difference (a-$\dot{V}O_2$D) was determined using the quotient of $\dot{V}O_2$ and $\dot{Q}$. Maximal exercise values for $\dot{Q}$ were estimated by multiplying the maximal HR by the SV obtained at 60% $\dot{V}O_{2peak}$. Although our methodology for estimating maximal $\dot{Q}$ using the theory that stroke volume plateaus at 60% $\dot{V}O_{2max}$ is derived from the results of two well-done studies (1,6,20), it should be noted that there is some evidence to

TABLE 2. Baseline values and changes with training at peak exercise.

Variable	Pretraining (Mean ± SD)	Posttraining (Mean ± SD)	Absolute Difference (post–pre)	Significant Difference $P < 0.05$
$\dot{V}O_2$ (mL·min^{-1})				
Premenopausal	1887 ± 361	2232 ± 387	345	*a*
Postmenopausal	1540 ± 268	1885 ± 329	345	*a, f*
No hormone	1552 ± 252	1872 ± 328	320	*a*
Hormone	1529 ± 286	1899 ± 335	370	*a*
HR (beats·min^{-1})				
Premenopausal	185.7 ± 12.5	186.6 ± 11.2	0.9	
Postmenopausal	168.3 ± 13.6	170.6 ± 10.6	2.3	*b, f*
No hormone	166.1 ± 11.9	168.9 ± 8.9	2.8	*b*
Hormone	170.4 ± 15.0	172.4 ± 12.0	2	
SV (mL·beat^{-1})				
Premenopausal	86.5 ± 14.8	94.7 ± 15.2	8.2	*a*
Postmenopausal	84.9 ± 11.6	93.6 ± 15.8	8.7	*a*
No hormone	84.8 ± 12.5	93.5 ± 15.2	9	*a*
Hormone	85.1 ± 10.8	93.8 ± 16.7	8.7	*a*
$\dot{Q}$ (L·min^{-1})				
Premenopausal	16.0 ± 2.7	17.7 ± 2.7	1.7	*a*
Postmenopausal	14.4 ± 2.0	16.1 ± 2.6	1.7	*a, f*
No hormone	14.3 ± 2.2	16.0 ± 2.5	1.7	*a*
Hormone	14.4 ± 1.9	16.2 ± 2.7	1.8	*a*
a-$\dot{V}O_2$D (mL/100 mL^{-1})				
Premenopausal	11.9 ± 1.7	12.7 ± 1.6	0.8	*a*
Postmenopausal	10.8 ± 1.5	11.9 ± 1.8	1.1	*a, f*
No hormone	10.9 ± 1.6	11.9 ± 1.5	1	*a*
Hormone	10.8 ± 1.4	12.0 ± 2.1	1.2	*a*
SBP (mm Hg)				
Premenopausal	181.3 ± 22.1	188.0 ± 22.6	6.7	*a*
Postmenopausal	198.2 ± 23.7	205.5 ± 25.2	7.3	*a, f*
No hormone	204.9 ± 20.3	211.1 ± 22.0	6.2	*a*
Hormone	190.9 ± 25.3	199.1 ± 27.4	8.2	*a, e*
DBP (mm Hg)				
Premenopausal	82.8 ± 12.4	79.0 ± 11.7	3.8	*a*
Postmenopausal	89.0 ± 12.0	86.8 ± 11.2	2.2	*a, f*
No hormone	90.2 ± 13.4	87.9 ± 11.2	2.3	*a*
Hormone	87.6 ± 12.5	85.6 ± 11.2	2	*a*
MAP (mm Hg)				
Premenopausal	115.6 ± 13.7	115.4 ± 12.8	0.2	
Postmenopausal	125.5 ± 13.3	126.4 ± 13.2	0.9	*f*
No hormone	128.5 ± 11.6	129.0 ± 10.7	0.5	
Hormone	122.3 ± 14.5	123.4 ± 15.3	1.1	
TPR (TPR units)				
Premenopausal	7.5 ± 1.5	6.7 ± 1.3	–0.8	*a*
Postmenopausal	9.0 ± 1.8	8.1 ± 1.5	–0.9	*a*
No hormone	9.2 ± 2.0	8.3 ± 1.6	–0.9	*a*
Hormone	8.7 ± 1.5	7.9 ± 1.5	–0.8	*a*
RER				
Premenopausal	1.17 ± 0.06	1.16 ± 0.05	–0.01	
Postmenopausal	1.17 ± 0.07	1.16 ± 0.07	–0.01	
No hormone	1.18 ± 0.07	1.16 ± 0.06	–0.02	
Hormone	1.17 ± 0.07	1.15 ± 0.08	–0.02	

[a] Significant training effect (posttraining value minus pretraining value).
[b] Significant difference in mean change with training vs premenopausal group.
[c] Significant difference in mean change with training vs no hormone group.
[d] Significant difference vs premenopausal group at baseline: covariance analysis.
[e] Significant difference vs no hormone group at baseline.
[f] Significant influence of age vs premenopausal group at baseline: covariance analysis.

suggest that stroke volume may not plateau at 60% $\dot{V}O_{2max}$. This estimate, therefore, should be interpreted with caution.

For the steady state periods in the submaximal test and the submaximal portion of the submax-to-max test, two $\dot{Q}$, HR, SBP, and DBP measurements were obtained, with the average of the two measurements being recorded as data points. Maximal exercise data were derived from an average of the means of the values from the initial maximal test and the submax-to-max test. All three protocols were repeated after the exercise training regimen, and were identical in every respect to the ones carried out during initial testing. The reproducibility coefficients of the assessments described above range from 0.76 to 0.99, demonstrating adequate reliability of measurement (30). Mean arterial pressure (MAP) was approximated as follows: (SBP + (2 × DBP))/3 (11). Total peripheral resistance (TPR) was estimated as MAP/$\dot{Q}$ (10). As is the case with the estimate of maximum $\dot{Q}$, these types of indirect estimates appear with considerable frequency in contemporary literature but should be interpreted with a degree of circumspection (30).

Exercise training regimen. The endurance training intervention was conducted on cycle ergometers (Universal Aerobicycle, Cedar Rapids, IA) in combination with a computer system (Universal Gym, Cedar Rapids, IA), which controlled ergometer power output, thereby allowing for the maintenance of a constant training HR. Training intensity was initially set at a HR equivalent to 55% of each subject's $\dot{V}O_{2peak}$ for 30 min·d^{-1} with a frequency of 3 d·wk^{-1}. By the end of the 14th week of training, the intensity and duration of the exercise bouts had progressed to 75% of $\dot{V}O_{2peak}$ for 50 min·d^{-1}, which was maintained throughout the remaining 6 wk of the regimen. At the end of the 20-wk regimen, subjects completed a battery of tests identical to those completed at study onset.

Research Design and Statistical Analysis

All data were analyzed using the SAS statistical package (version 6.12, SAS Institute, Inc., Cary, NC). A matched-pair *t*-test was used to determine significant differences between pre- and posttraining data, and ANCOVA was used to test for differences between pre- and postmenopausal women at baseline after adjusting the measurements for the influence of age. It should be noted that using ANCOVA to test for differences between family members (i.e., between mother and daughter) may violate the assumption of independent samples associated with the statistic. However, no other statistic affords the ability to control for age, and any analysis of this type without age being accounted for would be meaningless. Multiple testing ANOVA using the general linear models procedure was used to check for differences in training adaptation magnitudes among all subject stratifications and for differences at baseline attributable to hormone replacement. Since there was a significant discrepancy in subject number between pre- and postmenopausal women, a folded *F* test (*F'*) was conducted to test for homogeneity of variance between the pre- and postmenopausal groups with respect to the primary hemodynamic variables. The results indicated no significant differences in the variances of any of the variables tested. Comparison-wise error rate was set at the 0.05 level. Statistical power for hormone replacement group comparisons of hemodynamic data in the postmenopausal women, determined on the basis of the supposition of a moderate effect size, ranges from 0.61 to 0.74 (19). For all

other comparisons, similar table references show power calculations to be 0.89 or greater.

RESULTS

Hormone replacement influences. The multiple ANOVA procedure revealed that pretraining SBP measured at maximal exercise was 14 mm Hg less in postmenopausal women taking hormones than in those not taking hormones. Also, as a result of training, postmenopausal women not taking hormones experienced a greater reduction in SBP at 50 W (−23.4 vs 9.6 mm Hg) as well as slightly greater reductions in MAP and TPR. As can be seen in Tables 2 through 4, none of the other variables demonstrated significant differences related to hormone replacement status.

Menopause influences. Significant age-adjusted menopausal status differences were seen before exercise training. Pretraining SBP at 50 W, pretraining SBP at 60% $\dot{V}O_{2peak}$, and pretraining TPR at 60% $\dot{V}O_{2peak}$ were 26.2, 12.8, and 2.4 mm Hg·L^{-1}·min^{-1} lower, respectively, in the premenopausal women. Although several menopause-related differences in the magnitudes of training adaptations were statistically significant, the only one to approach physiological importance was the 7.5-mm Hg larger reduction of SBP seen in the postmenopausal women at 50 W. It is noteworthy that in the covariance analysis, the age covariate proved to be significant in most of the reported variables. Menopause differences between group means, unadjusted for age, are depicted in Tables 2 through 4.

Training-induced adaptations. As detailed earlier, exercise training produced slightly different results in women taking hormones versus those not taking hormones. However, cursory analysis of the data revealed that all but one of these differences (SBP at 50 W) were minor and physiologically inconsequential. Therefore, a better examination of training adaptations in postmenopausal women is afforded by the analysis of the postmenopausal group as a whole. For this group, peak exercise values for $\dot{V}O_2$, $\dot{Q}$, SV, a-$\dot{V}O_2$D, and SBP were increased with training, whereas TPR was reduced. Corresponding variables in the premenopausal group showed similar adaptive changes. These changes in relation to hemodynamic and oxygen uptake relationships are graphically depicted in Figure 1.

Analysis of measurements for the absolute power output of 50 W showed that in the postmenopausal women, $\dot{V}O_2$ and $\dot{Q}$ were both reduced less than 5% as a consequence of training. On the other hand, the 11.6% reduction in HR accompanied by the 7.6% increase in SV suggests a classic adaptation to an exercise training regimen. Changes in these same variables for premenopausal women were similar. Examination of pressure-flow dynamics in the postmenopausal group revealed that SBP, DBP, and MAP were all significantly reduced at 50 W, whereas TPR was diminished only slightly. Similar changes were seen in the premenopausal group. However, unlike postmenopausal women, TPR at 50 W in premenopausal women remained unchanged with training. Figure 2 depicts the training-induced changes at 50 W power output in terms of hemodynamic and oxygen uptake relationships for both pre- and postmenopausal women.

In postmenopausal women, assessment of training-induced changes at 60% $\dot{V}O_{2peak}$ showed a 7.1% increase in $\dot{Q}$ as well as a 6.5% increase in a-$\dot{V}O_2$D, both of which contributed to the 14.0% increase in absolute $\dot{V}O_2$ for that particular exercise intensity. Training adaptations were also seen, as HR was lower and SV higher. Although the increase in $\dot{V}O_2$ with training was significantly greater in the premenopausal women, the difference was not of physiologic

TABLE 3. Baseline values and changes with training at 50 W.

Variable	Pretraining (Mean ± SD)	Posttraining (Mean ± SD)	Absolute Difference (post–pre)	Significant Difference $P < 0.05$
$\dot{V}O_2$ (mL·min^{-1})				
Premenopausal	987 ± 115	945 ± 101	–42	*a*
Postmenopausal	1006 ± 96	981 ± 99	–25	*a, f*
No hormone	1015 ± 91	977 ± 99	–38	*a*
Hormone	996 ± 101	985 ± 100	–11	*a*
HR (beats·min^{-1})				
Premenopausal	131.1 ± 16.0	117.8 ± 12.0	–13.3	*a*
Postmenopausal	128.9 ± 14.2	114.0 ± 11.2	–14.9	*a*
No hormone	127.3 ± 13.3	112.3 ± 12.8	–15	*a*
Hormone	130.7 ± 15.2	115.9 ± 11.5	–14.8	*a*
SV (mL·beat^{-1})				
Premenopausal	86.3 ± 14.5	89.8 ± 13.2	3.5	*a*
Postmenopausal	85.2 ± 12.9	91.7 ± 14.3	6.5	*a*
No hormone	85.9 ± 14.0	92.7 ± 12.1	6.8	*a*
Hormone	84.4 ± 12.0	90.8 ± 16.6	6.4	*a*
$\dot{Q}$ (L·min^{-1})				
Premenopausal	11.2 ± 1.4	10.5 ± 1.3	–0.7	*a*
Postmenopausal	10.8 ± 1.5	10.4 ± 1.4	–0.4	*a*
No hormone	10.8 ± 1.5	10.3 ± 1.2	–0.5	*a*
Hormone	10.9 ± 1.4	10.4 ± 1.6	0.4	*a*
a-$\dot{V}O_2$D (mL/100 mL)				
Premenopausal	8.9 ± 1.0	9.1 ± 1.0	0.2	
Postmenopausal	9.4 ± 1.1	9.6 ± 1.1	0.2	*f*
No hormone	9.6 ± 1.2	9.6 ± 0.9	0	
Hormone	9.2 ± 0.9	9.6 ± 1.2	0.4	
SBP (mm Hg)				
Premenopausal	145.0 ± 19.2	136.0 ± 17.0	–9	*a*
Postmenopausal	171.2 ± 26.3	154.7 ± 20.6	–16.5	*a, b, d, f*
No hormone	180.1 ± 25.8	156.7 ± 21.7	–23.4	*a*
Hormone	162.0 ± 23.9	152.4 ± 19.5	–9.6	*a, c*
DBP (mm Hg)				
Premenopausal	72.8 ± 11.7	67.7 ± 10.7	–5.1	*a*
Postmenopausal	84.0 ± 10.4	77.3 ± 10.1	–6.7	*a, f*
No hormone	85.5 ± 10.8	77.0 ± 9.7	–8.5	*a*
Hormone	82.5 ± 9.9	77.6 ± 10.7	–4.9	*a*
MAP (mm Hg)				
Premenopausal	96.9 ± 13.1	90.5 ± 11.9	–6.4	*a*
Postmenopausal	113.1 ± 13.8	103.3 ± 12.2	–9.8	*a, b, f*
No hormone	117.0 ± 14.3	104.0 ± 12.5	–13	*a*
Hormone	108.9 ± 12.2	102.6 ± 12.1	–6.3	*a, c*
TPR (TPR units)				
Premenopausal	8.8 ± 1.4	8.8 ± 1.5	0	
Postmenopausal	10.6 ± 2.0	10.1 ± 1.6	–0.5	*b, f*
No hormone	11.1 ± 2.2	10.2 ± 1.6	–0.9	
Hormone	10.1 ± 1.7	9.9 ± 1.5	–0.2	*c*

[a] Significant training effect (posttraining value minus pretraining value).
[b] Significant difference in mean change with training vs premenopausal group.
[c] Significant difference in mean change with training vs no hormone group.
[d] Significant difference vs premenopausal group at baseline: covariance analysis.
[e] Significant difference vs no hormone group at baseline.
[f] Significant influence of age vs premenopausal group at baseline: covariance analysis.

TABLE 4. Baseline values and changes with training at 60% of $\dot{V}O_{2max}$.

Variable	Pretraining (Mean ± SD)	Posttraining (Mean ± SD)	Absolute Difference (post–pre)	Significant Difference $P < 0.05$
$\dot{V}O_2$ (mL·min^{-1})				
Premenopausal	1145 ± 231	1323 ± 243	178	*a*
Postmenopausal	951 ± 183	1085 ± 223	134	*a, b, f*
No hormone	946 ± 190	1066 ± 207	120	*a*
Hormone	957 ± 179	1106 ± 243	149	*a*
HR (beats·min^{-1})				
Premenopausal	142.4 ± 16.9	139.8 ± 14.5	–2.6	*a*
Postmenopausal	124.3 ± 13.3	119.4 ± 11.2	–4.9	*a, f*
No hormone	122.7 ± 12.6	117.1 ± 9.1	–5.6	*a*
Hormone	125.9 ± 14.0	122.0 ± 12.9	–3.9	*a*
SV (mL·beat^{-1})				
Premenopausal	86.5 ± 14.9	94.7 ± 15.2	8.2	*a*
Postmenopausal	84.9 ± 11.6	93.6 ± 15.8	8.7	*a*
No hormone	84.8 ± 12.5	93.5 ± 15.2	8.7	*a*
Hormone	85.1 ± 10.8	93.8 ± 16.7	8.7	*a*
$\dot{Q}$ (L·min^{-1})				
Premenopausal	12.2 ± 2.0	13.2 ± 2.1	1	*a*
Postmenopausal	10.4 ± 1.9	11.2 ± 1.9	0.8	*a, f*
No hormone	10.4 ± 2.0	10.9 ± 1.9	0.5	*a*
Hormone	10.5 ± 1.8	11.5 ± 2.0	1	*a*
a-VO_2D (mL/100 mL)				
Premenopausal	9.4 ± 1.2	10.1 ± 1.2	0.7	*a*
Postmenopausal	9.3 ± 1.1	9.9 ± 1.3	0.6	*a*
No hormone	9.3 ± 1.2	9.9 ± 1.0	0.6	*a*
Hormone	9.3 ± 0.9	9.8 ± 1.5	0.5	*a*
SBP (mm Hg)				
Premenopausal	152.6 ± 16.9	153.0 ± 18.0	0.4	
Postmenopausal	165.4 ± 20.2	162.9 ± 23.2	–2.5	*b, d, f*
No hormone	171.2 ± 19.8	166.9 ± 24.8	–4.3	
Hormone	159.3 ± 19.0	158.3 ± 20.8	–1	
DBP (mm Hg)				
Premenopausal	73.8 ± 11.7	68.2 ± 10.8	–5.6	*a*
Postmenopausal	83.1 ± 10.0	77.0 ± 10.2	–6.1	*a, f*
No hormone	84.1 ± 10.6	77.0 ± 10.4	–7.1	*a*
Hormone	82.1 ± 9.5	76.9 ± 10.2	5.2	*a*
MAP (mm Hg)				
Premenopausal	100.0 ± 11.8	96.5 ± 11.5	–3.5	*a*
Postmenopausal	110.6 ± 11.4	105.7 ± 12.5	–4.9	*a, f*
No hormone	113.1 ± 11.6	107.0 ± 12.7	–6.1	*a*
Hormone	107.8 ± 10.6	104.3 ± 12.5	–3.5	*a*
TPR (TPR units)				
Premenopausal	8.5 ± 1.8	7.5 ± 1.5	–1	*a*
Postmenopausal	10.9 ± 2.1	9.7 ± 1.8	–1.2	*a, d, f*
No hormone	11.3 ± 2.3	10.1 ± 2.1	–1.2	*a*
Hormone	10.5 ± 1.9	9.3 ± 1.3	–1.2	*a*

[a] Significant training effect (posttraining value minus pretraining value).
[b] Significant difference in mean change with training vs premenopausal group.
[c] Significant difference in mean change with training vs no hormone group.
[d] Significant difference vs premenopausal group at baseline: covariance analysis.
[e] Significant difference vs no hormone group at baseline.
[f] Significant influence of age vs premenopausal group at baseline: covariance analysis.

importance. As was the case at 50 W, indicators of pressure and resistance in both the postmenopausal and premenopausal women, save SBP, showed a significant training-associated reduction. These training-induced changes are graphically illustrated in Figure 3.

DISCUSSION

Hormone replacement influences. One objective of this study was to determine if any hemodynamic-related differences during exercise existed between postmenopausal women taking hormones versus those not taking hormones. Such differences were expected because of previous findings suggesting that the estrogen in the hormone supplements would reduce overall TPR (2,3,12), thereby facilitating higher $\dot{Q}$ levels (5). The only hormone replacement-related difference found was that postmenopausal women taking hormones had a 14-mm Hg lower pretraining SBP during peak exercise. Although corresponding TPR and estimated cardiac index (a *post hoc* variable that normalizes $\dot{Q}$ by dividing it by body surface area) were also about 5% lower and 6% higher, respectively, the values did not reach statistical significance. It should again be noted, however, that our assessment of $\dot{Q}$ at peak exercise was an estimate and that comparisons along this line to previous research should be viewed accordingly.

Our results are directly supported by a study conducted by Pines et al. in which changes in SBP from rest to maximal exercise became smaller after a regimen of hormone replacement (18). The results of a related study by Lewandowski and colleagues (9) lend further affirmation to our findings. In their study, SBP taken while working on a

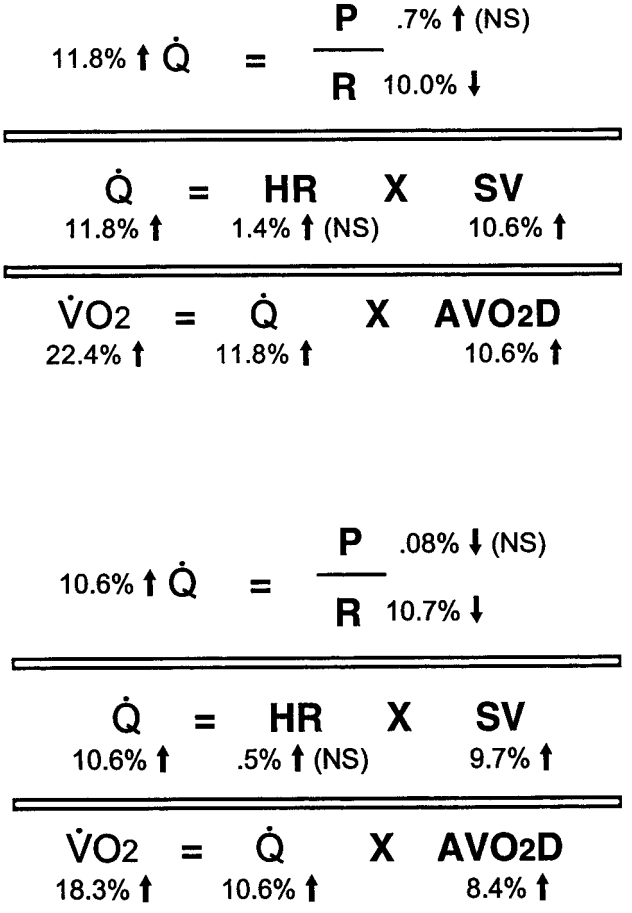

FIGURE 1—Training-induced changes in hemodynamics and Fick variables during peak exercise in postmenopausal (*top panel*) and premenopausal (*bottom panel*) women. $\dot{Q}$, cardiac output; P, mean arterial pressure; R, total peripheral resistance; HR, heart rate; SV, stroke volume; $\dot{V}O_2$, oxygen consumption; A$\dot{V}O_2$D, arteriovenous oxygen difference.

treadmill at 80% $\dot{V}O_{2max}$ was found to be 14 mm Hg lower in a group of ovariectomized women taking supplemental estrogen versus ovariectomized women not taking estrogen. This led the authors to hypothesize that the pressor response in ovariectomized estrogen-treated women was lower during high levels of exercise than in ovariectomized women not treated with estrogen. Here again, we see evidence that estrogen supplementation may be involved in improving arterial compliance during high levels of exercise. Additional support for this hypothesis is gleaned from a randomized double-blind crossover study by Snabes and colleagues (24). In this particular study, supplemental estrogen was associated with a pulmonary artery pressure at maximal exercise that was 4 mm Hg lower during the hormone administration trial. The authors hypothesized that this might reflect a vasodilatory effect of estrogen on the pulmonary resistance vessels.

Our current results, along with those discussed above and the significant reduction in TPR seen in the lead author's earlier work (5), suggest that a vasodilatory or compliance "reserve" is present in women taking estrogen and that this reserve becomes apparent only under conditions of high oxygen demand. It is also possible that the progesterone content of the hormone replacement regimen in our study, as well as that of the other studies described above, was responsible for the lack of a larger reduction in TPR at maximal exercise and, concomitantly, the lack of statistical significance. Although most studies show the effects of progesterone on hemodynamic factors to be negligible (4,8,15,23), some suggest a significant attenuation of estrogen-mediated vasodilation and resistance reduction (14,21), which may have influenced our results. This same confounding factor, as well as inadequate statistical power, may have affected the results of a recent study by McCole and colleagues (13) which suggest that hormone replacement does not significantly influence hemodynamics at maximal exercise.

In summary, our results compare favorably with those in the majority of the contemporary literature and, at least to a small extent, suggest that hormone replacement therapy enhances arterial compliance at high levels of exercise. It also seems clear, however, that hormone replacement does not significantly influence the hemodynamic responses to exercise at relatively lower submaximal power outputs.

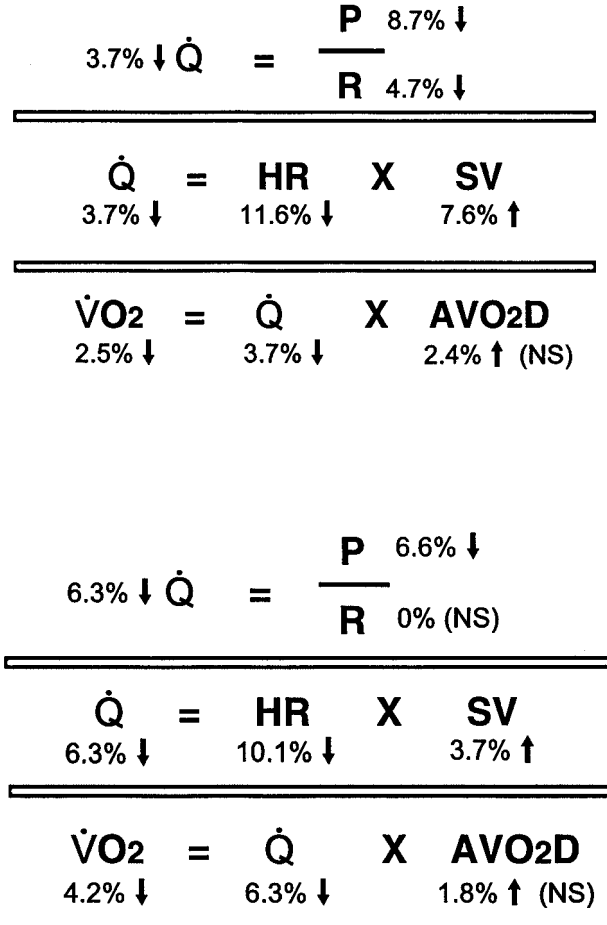

FIGURE 2—Training-induced changes in hemodynamics and Fick variables during exercise at 50 W in postmenopausal (*top panel*) and premenopausal (*bottom panel*) women. $\dot{Q}$, cardiac output; P, mean arterial pressure; R, total peripheral resistance; HR, heart rate; SV, stroke volume; $\dot{V}O_2$, oxygen consumption; AVO_2D, arteriovenous oxygen difference.

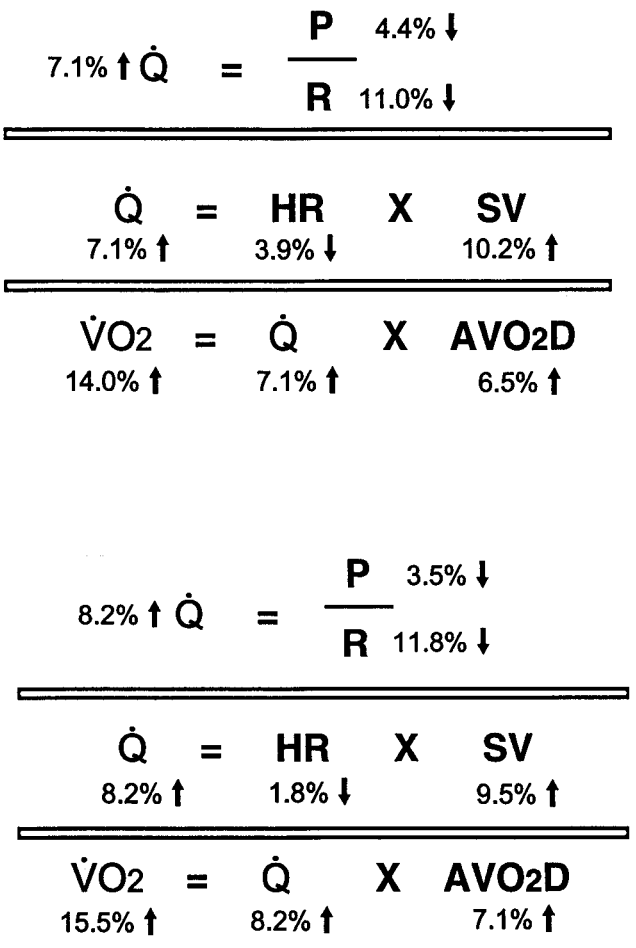

FIGURE 3—Training-induced changes in hemodynamics and Fick variables during exercise at 60% $\dot{V}O_{2max}$ in postmenopausal (*top panel*) and premenopausal (*bottom panel*) women. $\dot{Q}$, cardiac output; P, mean arterial pressure; R, total peripheral resistance; HR, heart rate; SV, stroke volume; $\dot{V}O_2$, oxygen consumption; AVO_2D, arteriovenous oxygen difference.

Menopause influences. There are few studies that address hemodynamic consequences of menopause during high levels of exercise. Those that exist are limited in scope, assessing only the customary variables of HR and $\dot{V}O_2$ (17,27). These studies report no menopause-related differences in these two particular measures, a finding that is supported by the results of our investigation. Other variables in our analysis, however, demonstrated significant menopausal discrepancies. Pretraining SBP at 50 W was 26.2 mm Hg lower in the premenopausal women, whereas pretraining SBP and TPR measured at 60% $\dot{V}O_{2peak}$ were 12.8 mm Hg and 2.4 mm $Hg \cdot L^{-1} \cdot min^{-1}$ lower, respectively. It should be noted, however, that after adjustment for age in the covariance analysis, SBP at 50 W was the only variable that retained physiological significance, with an age-adjusted difference of about 10 mm Hg. As alluded to earlier, no studies could be found with which to directly compare this finding, as most studies investigating the cardiovascular consequences of menopause are concerned only with cardiac risk factors and resting ventricular function. The only study even remotely related to ours showed DBP at maximal exercise to be 14 mm Hg lower in a group of women ages 40–45 versus women ages 58–63. However, all of the women were endurance trained, and menopausal status was not considered as an independent variable and thus was not verified. In addition, the substantial difference in subject age was not statistically controlled (28). Although our raw data show findings similar to those in the aforementioned study in that maximum SBP, DBP, and MAP were substantially lower in the premenopausal group, these differences almost disappear completely when age is statistically accounted for. As can be seen in Tables 2 through 4, the age covariate in our analysis was significant in a great majority of the variables measured, indicating that age may account for much of the decline in cardiovascular hemodynamic function that some attribute to menopause and the associated loss of endogenous estrogen.

It would be tempting to theorize that in the present study, the smaller age-adjusted SBP at 50 W seen in the premenopausal women was a result of greater arterial compliance related to the presence of endogenous estrogen. On the other hand, the lack of supporting literature coupled with the extraneous variation inherent in the cross-sectional nature of the hormone replacement component of our study makes this hypothesis somewhat premature. Clearly, further investigation into the effects of endogenous estrogen on cardiovascular hemodynamics during submaximal exercise is needed before definitive conclusions can be made.

Training-induced adaptations. As with submaximal power outputs, changes in hemodynamic parameters at maximal exercise after training were similar in both pre- and postmenopausal women. As depicted in Figure 1, all variables related to oxygen uptake and delivery, save HR, were increased, while peripheral resistance was reduced. Maximal MAP remained unaffected in both pre- and postmenopausal groups. The results of our investigation are in contrast to those of a landmark study by Spina and colleagues (25), who found that in postmenopausal women, a 22% increase in $\dot{V}O_{2max}$ was mediated entirely by a 18% increase in a-$\dot{V}O_2$D. Exercise training paradigms for both studies were similar, yielding approximately the same increase in $\dot{V}O_{2max}$ in both subject cohorts. However, we also saw an increase in $\dot{Q}$ consequent to an increase in SV, and the increase in a-$\dot{V}O_2$D in our study was about 7% less. These differences may be partly explained by the fact that the women in Spina's study were an average of almost 10 yr older than our postmenopausal subjects, which may have limited their adaptability to exercise training.

As can be seen in Figure 2, adaptations to training measured at an absolute submaximal power output were similar in both the pre- and postmenopausal groups, with the postmenopausal group showing a slightly smaller reduction in $\dot{V}O_2$ and $\dot{Q}$ accompanied by a slightly larger increase in SV. The reduction in absolute $\dot{V}O_2$ implies an increase in the efficiency of the subjects in pedaling the ergometer, while the reduction in HR and the concomitant increase in SV represent training adaptations previously documented in both younger and older women (7,22,25). These findings are somewhat similar to those of an early study by Kilbom and Åstrand (7), in which $\dot{V}O_2$ at 50 W was reduced in both young and old women by about 4% as a consequence of exercise training. As in our study, SBP and MAP at 50 W were reduced to a slightly greater extent in the older women.

Although not identical, training adaptation magnitudes at 60% $\dot{V}O_{2peak}$ were similar for both the pre- and postmenopausal women, with an increase in $\dot{Q}$ contributing to an increase in $\dot{V}O_2$. In both groups, HR was lower and SV higher after training, reflecting the reduction in afterload consequent to a reduction in peripheral resistance. An early study by Niinimaa and Shephard (16) examined hemodynamic changes at 60% $\dot{V}O_{2max}$ in 7 women aged 60–76 after 11 wk of endurance training and found no change in $\dot{V}O_2$, HR, $\dot{Q}$, SV, and a-$\dot{V}O_2$D. The authors attributed the lack of changes to the fact that $\dot{V}O_{2max}$ did not show a training-induced increase in their subjects. They went on to suggest that the reason no changes were seen in $\dot{V}O_{2max}$ was that the training regimen was too short and the subjects' original $\dot{V}O_{2max}$ was unusually high at study onset. In our study, all subjects were required to be previously sedentary which, in the postmenopausal women, for example, facilitated an 18.3% training-induced increase in peak exercise $\dot{V}O_2$. This, in turn, led to a 14% increase in $\dot{V}O_2$ at the 60% $\dot{V}O_{2peak}$ intensity. A better comparison to our data is afforded by a more contemporary study by Seals et al. (22). In their study, a 12-month endurance training regimen conducted on seven men and four women (mean age, 63 yr) elicited a 25% increase in $\dot{V}O_{2max}$ and a concomitant 23% increase in $\dot{V}O_2$ at 60% $\dot{V}O_{2max}$. In accordance with our study, MAP and TPR were both reduced, whereas SV was increased. Unfortunately, data for the women were not analyzed separately; therefore, direct comparison with data from our study is not possible.

In conclusion, our data suggest that hormone replacement influences on cardiovascular hemodynamics during exercise in postmenopausal women are limited to instances of high exercise intensity. Specifically, since SBP at peak exercise

in women taking hormones was found to be less than in women not taking hormones at almost identical levels of $\dot{V}O_2$ and $\dot{Q}$, it is possible that hormone replacement facilitates a "vasodilatory reserve" that becomes apparent only at or near peak exercise. This observation is most certainly preliminary and requires further investigation with well-controlled longitudinal experiments before any definitive conclusions can be made. Furthermore, after adjustment for age, menopause has no significant effects on exercise hemodynamics in women, save a smaller SBP in the premenopausal women at an absolute power output. However, since there is little support in the literature for attributing this finding to hormone replacement, confident speculation to that effect cannot be made at this juncture. Finally, exercise training improves exercise hemodynamic function in women of all ages, with no substantial physiologic differences with respect to menopausal or hormone replacement status. This is demonstrated by reductions in cardiac and oxygen demand at an absolute submaximal power output, as well as possible enhancements of oxygen delivery mechanisms at maximal power output.

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Address for correspondence: John S. Green, Ed.D., Ph.D., FACSM, Department of Health and Kinesiology, TAMU 4243-113 Netum Steed Building, Texas A&M University, College Station, TX 77843-4243; E-mail: jsgreen@tamu.edu.

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