$\dot{V}O_{2max}$ is associated with ACE genotype in postmenopausal women

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Hagberg, James M., Robert E. Ferrell, Steve D. McCole, Kenneth R. Wilund, and Geoffrey E. Moore. $\dot{V}O_{2max}$ is associated with ACE genotype in postmenopausal women. *J. Appl. Physiol.* 85(5): 1842–1846, 1998.—Relationships have frequently been found between angiotensin-converting enzyme (ACE) genotype and various pathological and physiological cardiovascular outcomes and functions. Thus we sought to determine whether ACE genotype affected maximal O_2 consumption ($\dot{V}O_{2max}$) and maximal exercise hemodynamics in postmenopausal women with different habitual physical activity levels. Age, body composition, and habitual physical activity levels did not differ among ACE genotype groups. However, ACE insertion/insertion (II) genotype carriers had a 6.3 $ml \cdot kg^{-1} \cdot min^{-1}$ higher $\dot{V}O_{2max}$ ($P < 0.05$) than the ACE deletion/deletion (DD) genotype group after accounting for the effect of physical activity levels. The ACE II genotype group also had a 3.3 $ml \cdot kg^{-1} \cdot min^{-1}$ higher $\dot{V}O_{2max}$ ($P < 0.05$) than the ACE insertion/deletion (ID) genotype group. The ACE ID group tended to have a higher $\dot{V}O_{2max}$ than the DD genotype group, but the difference was not significant. ACE genotype accounted for 12% of the variation in $\dot{V}O_{2max}$ among women after accounting for the effect of habitual physical activity levels. The entire difference in $\dot{V}O_{2max}$ among ACE genotype groups was the result of differences in maximal arteriovenous O_2 difference (a-vDO_2). ACE genotype accounted for 17% of the variation in maximal a-vDO_2 in these women. Maximal cardiac output index did not differ whatsoever among ACE genotype groups. Thus it appears that ACE genotype accounts for a significant portion of the interindividual differences in $\dot{V}O_{2max}$ among these women. However, this difference is the result of genotype-dependent differences in maximal a-vDO_2 and not of maximal stroke volume and maximal cardiac output.

maximal cardiac output; postmenopausal women; women athletes; body

MAXIMAL O_2 CONSUMPTION ($\dot{V}O_{2max}$) is an important clinical and physiological parameter because it is associated with critical variables that range from cardiovascular (CV) disease risk to performance in endurance-based competitive athletic events (2, 5, 6, 17). $\dot{V}O_{2max}$ varies widely among individuals, and a person's habitual physical activity levels clearly account for a substantial proportion of these interindividual differences. However, after accounting for the effect of different habitual levels of physical activity, there is still substantial variability in $\dot{V}O_{2max}$ among individuals. Clearly, genetic factors also play a role in determining a person's $\dot{V}O_{2max}$ (3). However, at present, only polymorphic variations that occur infrequently (4) or that have not been substantiated in other studies (12) have been shown to affect $\dot{V}O_{2max}$.

A polymorphic insertion/deletion (ID) variation in intron 16 of the angiotensin-converting enzyme (dipeptidyl carboxypeptidase 1; ACE) gene locus was identified over 15 yr ago. Individuals with the ACE deletion/deletion (DD) genotype have higher plasma, cardiac tissue, and lymphocyte ACE levels than do ACE insertion/insertion (II) carriers (15, 18). A recent study found that ACE genotype also affects the physiological left ventricular (LV) hypertrophy resulting from endurance exercise training (10). The renin-angiotensin system, which ACE is a component of, also has a profound effect on the structure and function of the peripheral vascular system (15). Furthermore, a recent abstract (19) reported an altered distribution of ACE alleles and genotypes in Australian Olympic rowers compared with the general population. In addition, the DD genotype at this locus has been found to be associated with increased CV disease risk (14). Because $\dot{V}O_{2max}$ is an independent risk factor for CV disease (2), it is possible that ACE genotype may exert its effect on CV disease risk by affecting $\dot{V}O_{2max}$. Therefore, we hypothesized that ACE genotype would affect a person's $\dot{V}O_{2max}$ and that it would do so by affecting maximal stroke volume and maximal cardiac output.

METHODS

Postmenopausal women were studied in our laboratory to assess the effects of habitual physical activity and hormone-replacement therapy (HRT) on $\dot{V}O_{2max}$ and maximal exercise hemodynamics. All women provided written informed consent to participate; the study was approved by the University of Pittsburgh Institutional Review Board. Sedentary and physically active postmenopausal women were recruited from the Pittsburgh metropolitan area, and elite endurance-trained postmenopausal women athletes were recruited from across the United States. "Sedentary" was defined as not regularly taking part in any aerobic types of exercise. "Physically active" was defined as meeting recent physical activity guidelines for the American population (at least 30 min/day of low- to moderate-intensity physical activity most days of the week; Ref. 11) but not training for competitive events. The

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athletes were all training intensely and regularly for endurance-based competitive running events. "Postmenopausal" was defined as the reported lack of menstrual cycles for >2 yr, along with elevated levels of follicle-stimulating and luteinizing hormones. Approximately one-half of the women in each physical-activity group were on HRT and one-half were not. The habitual physical activity levels and HRT programs of the women had remained constant for >2 yr before the study.

Sedentary and physically active women initially underwent a screening maximal treadmill exercise test to ensure they had no evidence of CV disease (1). Those with no detectable CV disease underwent a second maximal treadmill test to assess $\dot{V}O_{2max}$. The second test began at a treadmill speed set to elicit 60% of the peak oxygen uptake ($\dot{V}O_2$) achieved in their screening test. After the first 2 min on a level treadmill, treadmill grade increased to 4% and then increased 2% every 2 min until the subject was unable to continue.

Because of the low likelihood of CV disease in the athletes, they underwent a single test for screening and measurement of $\dot{V}O_{2max}$. After a thorough warm-up and familiarization, women athletes began running on a level treadmill at a speed slightly below their 10-km race pace. Treadmill grade increased by 2% every 2 min until the subjects were unable to continue. During these tests, $\dot{V}O_2$ was measured every 30 s by using a customized, validated, computer-based system using a Marquette respiratory mass spectrometer, a Rudolph low-volume breathing valve, a Rayfield mixing chamber, and an Interface Associates VMM turbine volume meter. To ensure that a true $\dot{V}O_{2max}$ was measured, three of the following four standard criteria had to be achieved: a leveling off of $\dot{V}O_2$ (<150 ml/min increase in the last 2 min), a respiratory exchange ratio >1.10, a maximal heart rate within 10 beats/min of predicted maximal (220 beats/min − years of age), and a $\dot{V}O_2$ requirement for the final stage that exceeded the measured $\dot{V}O_2$ (16). Tests not meeting these criteria were repeated. In addition, all subjects had their body composition measured with a Lunar DPX-L dual-energy X-ray absorptiometer.

All subjects also had their maximal cardiac output assessed during treadmill exercise by using a computer-based acetylene rebreathing system developed in our laboratory. Technically acceptable data were available from 47 of the total of 58 women. $\dot{V}O_2$ was also measured during this test so that maximal arteriovenous O_2 difference (a-vDO_2) could be calculated from $\dot{V}O_2$ and cardiac output. Heart rate and blood pressure were also measured immediately before the rebreathing maneuver so that stroke volume and total peripheral resistance at maximal exercise could be calculated. However, in some cases, blood pressure could not be measured during exercise and was measured in the first minute of recovery. The data comparing $\dot{V}O_{2max}$ and maximal exercise hemodynamics among the different habitual physical activity groups will be presented elsewhere.

High-molecular-weight genomic DNA was isolated from EDTA-anticoagulated whole blood by standard procedures (9). Subjects were genotyped for the ACE intron 16 Alu insertion by the method of Tiret et al. (18). The I (insertion) allele yields a fragment of 490 bp, and the D (deletion) allele yields a product of 190 bp. Heterozygotes were characterized by the presence of both bands plus a slower migrating heteroduplex. Alleles were scored by direct comparison to sequence-verified controls run on the same gel, and subjects were charaterized as II, ID, or DD carriers.

Data are means ± SD. Because subjects with a range of habitual physical activity levels were included in this study and because physical activity levels affect a number of the variables of interest in this study, each subject's values were first expressed as a difference from the average value for that variable for their physical activity group. These difference values were then normalized by dividing by the SD for their respective physical activity group, and ANOVAs with Fisher least significant difference post hoc tests were performed to compare the normalized difference variables among genotype groups. The statistical results for the analyses based on absolute values paralleled those for these normalized values. Thus the data are presented as absolute values to make the results more physiologically meaningful. Pearson correlation coefficients were calculated to assess the strength of statistical relationships. A probability of <0.05 was accepted as statistically significant.

Table 1. *Distribution of ACE genotypes in the total group of postmenopausal women and in the individual groups with different habitual levels of physical activity*

Subject Group	ACE Genotype		
	II, %	ID, %	DD, %
Total group	21 (n = 12)	57 (n = 33)	22 (n = 13)
Sedentary women	26 (n = 5)	48 (n = 9)	26 (n = 5)
Physically active women	16 (n = 3)	63 (n = 12)	21 (n = 4)
Women athletes	20 (n = 4)	60 (n = 12)	20 (n = 4)

n, No. of subjects. ACE, angiotensin-converting enzyme; II, insertion/insertion; ID, insertion/deletion; DD, deletion/deletion.

RESULTS

The distribution of ACE genotypes in this group of 58 postmenopausal women was 21% II, 57% ID, and 22% DD (Table 1), which is similar to the distribution in the general population (II: 23%, ID: 49%, DD: 28%; Ref. 14). Although the sample sizes were small, the distribution of ACE genotypes did not differ among the habitual physical activity groups.

Age, the number of years the women had been postmenopausal, and HRT duration did not differ among ACE genotype groups (Table 2). The HRT history of the women differed somewhat among genotype groups (DD: 4 on, 9 not on HRT; ID 15 on, 18 not on HRT; II: 9 on, 3 not on HRT). However, we have previously shown in these women that HRT did not affect $\dot{V}O_{2max}$ (unpublished observations). For the physically active women

Table 2. *Characteristics of the three ACE genotype groups of postmenopausal women*

ACE Genotype	Age, yr	Years Post-menopausal	HRT Duration,* yr	PA per wk,† h	PA History,† yr	Running Mileage,‡ miles/wk
II	62 ± 3	17 ± 9	9 ± 6	5.5 ± 1.7	12 ± 7	28 ± 12
ID	63 ± 5	16 ± 9	9 ± 6	5.2 ± 2.1	14 ± 6	31 ± 9
DD	65 ± 5	11 ± 5	19 ± 13	5.3 ± 2.1	15 ± 4	26 ± 9

Values are means ± SD. All subjects included in averages for age and years postmenopausal. *Values averaged only for women on hormone-replacement therapy (HRT); †values averaged only for physically active (PA) and endurance-trained athlete subjects; ‡values averaged only for endurance-trained athletes. None of differences among ACE genotype groups was statistically significant.

Table 3. *Body composition characteristics of the three ACE genotype groups of postmenopausal women*

ACE Genotype	Height, cm	Body Weight, kg	Body Fat, %	Fat Mass, kg	Fat-Free Mass, kg
II ($n = 12$)	159 ± 9	59.1 ± 7.0	30.4 ± 8.9	18.1 ± 6.2	40.9 ± 6.6
ID ($n = 33$)	160 ± 5	60.1 ± 9.2	32.9 ± 8.3	20.3 ± 7.6	39.8 ± 3.9
DD ($n = 13$)	159 ± 8	60.3 ± 8.5	33.9 ± 8.7	20.9 ± 7.4	39.4 ± 3.9

Values are means ± SD; n, no. of subjects. None of the differences between ACE genotype groups was significant for any of these variables.

and athletes, the physical activity per week and the number of years of physical activity did not differ among ACE genotype groups. Running mileage per week also did not differ among the women athletes in the different ACE genotype groups.

Height, weight, percent body fat, fat mass, and fat-free mass did not differ among the three ACE genotype groups (Table 3). After accounting for the independent effect of habitual physical activity level on $\dot{V}O_{2max}$, the ACE II genotype group had a $\dot{V}O_{2max}$ that was 6.3 $ml \cdot kg^{-1} \cdot min^{-1}$ (23%) higher than the ACE DD genotype group (Table 4). The ACE II genotype group also had a 3.3 $ml \cdot kg^{-1} \cdot min^{-1}$ (11%) higher $\dot{V}O_{2max}$ than the ACE ID genotype group after accounting for the effect of habitual physical activity level. The ACE ID group tended to have a higher $\dot{V}O_{2max}$ than the DD genotype group, but the difference was not significant. The interaction term between ACE genotype and physical activity level in the ANOVA was not significant ($P = 0.37$), indicating that the effect of ACE genotype on $\dot{V}O_{2max}$ was relatively consistent across the groups with different habitual physical activity levels (Table 4). The respiratory exchange ratio at maximal exercise did not differ significantly among ACE genotype groups (II 1.16 ± 0.07, ID 1.21 ± 0.10, and DD 1.19 ± 0.08; $P = 0.25$), providing evidence that women in all genotype groups reached the same level of exertion during the $\dot{V}O_{2max}$ test. Habitual physical activity levels accounted for 71% of the interindividual variation in $\dot{V}O_{2max}$ in these 58 women. After accounting for the effect of habitual physical activity level on $\dot{V}O_{2max}$, ACE genotype accounted for another 12% of the interindividual variation in $\dot{V}O_{2max}$ among these women.

Table 4. *$\dot{V}O_{2max}$ of postmenopausal women in the different ACE genotype groups in the total population and the different habitual physical activity groups*

	$\dot{V}O_{2max}$, $ml \cdot kg^{-1} \cdot min^{-1}$			
ACE Genotype	Total group	Sedentary women	Physically active women	Women athletes
II	33.4 ± 7.6†	28.6 ± 4.0	28.1 ± 2.9	40.5 ± 6.1
ID	30.1 ± 8.5*	22.6 ± 3.2	26.1 ± 2.6	39.6 ± 5.7
DD	27.1 ± 5.8*	23.3 ± 2.0	24.5 ± 1.7	34.8 ± 3.4

Values are means ± SD. $\dot{V}O_{2max}$, maximal O_2 consumption. Values for total group ACE genotype groups with different symbols following them are significantly different at $P < 0.05$. Statistical analyses were not performed to compare $\dot{V}O_{2max}$ values across different ACE genotype groups with different habitual PA groups.

The entire difference in $\dot{V}O_{2max}$ between ACE genotype groups was the result of differences in maximal a-vD_{O_2}, which was greatest in ACE II genotype women, intermediate in heterozygotes, and lowest in ACE DD genotype women (Table 5). Maximal a-vD_{O_2} for the entire population was 15.4 ± 1.7 ml O_2/100 ml, and the difference between the ACE II and DD groups amounted to 2.1 ml O_2/100 ml, or nearly 14% of the total group average value. Furthermore, ACE genotype accounted for 17% of the interindividual variation in maximal a-vD_{O_2} in these women. Maximal cardiac output index did not differ among ACE genotype groups. However, the similar maximal cardiac output was achieved via somewhat different mechanisms in the three genotype groups, since maximal heart rate was higher by 10 beats/min in the ACE II than in the ACE ID and DD genotype groups, whereas maximal stroke volume index was somewhat lower in the ACE II than in the ACE ID and DD genotype groups. Total peripheral resistance at maximal exercise did not differ significantly between ACE genotype groups.

DISCUSSION

$\dot{V}O_{2max}$ is an important clinical and physiological variable because of it's close relationship with CV disease risk (2) and athletic performance in endurance-based competitive events (5, 6, 17). $\dot{V}O_{2max}$ is highly variable among individuals, and one primary determinant of $\dot{V}O_{2max}$ is one's habitual physical activity level. This is substantiated in the present study by the finding that, in these postmenopausal women with a wide range of habitual physical activity, levels of physical activity accounted for 71% of the interindividual variations in $\dot{V}O_{2max}$. The results of the present study further indicate, however, that ACE genotype accounts for an additional 12% of the interindividual variation in $\dot{V}O_{2max}$ in postmenopausal women. Age was not significantly different between ACE genotype groups, but, even if a liberal 1% per year difference in $\dot{V}O_{2max}$ is

Table 5. *Maximal exercise hemodynamics in different ACE genotype groups of postmenopausal women*

Genotype	Maximal Cardiac Output Index, $l \cdot min^{-1} \cdot m^{-2}$ BSA	Maximal Stroke Volume Index, ml/m^2 BSA	Maximal Heart Rate, beats/min	Maximal a-vD_{O_2}, ml/dl	Total Peripheral Resistance, $dyn \cdot s \cdot cm^{-5}$
II	6.8 ± 1.5 ($n = 10$)	39.9 ± 9.2 ($n = 10$)	173 ± 10† ($n = 12$)	16.5 ± 2.0† ($n = 10$)	904 ± 240 ($n = 10$)
ID	6.9 ± 1.4 ($n = 25$)	43.8 ± 9.1 ($n = 25$)	163 ± 12* ($n = 33$)	15.4 ± 1.6* ($n = 25$)	846 ± 202 ($n = 25$)
DD	6.8 ± 1.2 ($n = 12$)	41.8 ± 8.8 ($n = 12$)	162 ± 11* ($n = 13$)	14.4 ± 1.2* ($n = 12$)	862 ± 206 ($n = 12$)

Values are means ± SD; n, no. of subjects per sample. BSA, body surface area. Not all subjects had valid maximal exercise hemodynamic values; therefore, sample sizes for these comparisons (in parentheses) are smaller than those for $\dot{V}O_{2max}$. Same trends for genotype-dependent differences in $\dot{V}O_{2max}$ existed for smaller no. of subjects who had valid maximal exercise hemodynamic values. Values with different symbols following them are significantly different at $P < 0.05$. Variables without symbols following them are not significantly different.

assumed (7), age could at most account for a 3% difference in $\dot{V}O_{2max}$, whereas the differences between the genotype groups most widely disparate in age amounted to 23%. Contrary to our original hypothesis, ACE genotype was not related to maximal stroke volume or maximal cardiac output but was related to maximal a-vDO_2. The ACE II genotype group had the highest $\dot{V}O_{2max}$ with the largest maximal a-vDO_2; the ACE DD genotype group had the lowest values for both $\dot{V}O_{2max}$ and maximal a-vDO_2.

Previous research has clearly demonstrated that genetics play an important role in determining a person's $\dot{V}O_{2max}$. This evidence ranges from the association of $\dot{V}O_{2max}$ values within families and a greater similarity for $\dot{V}O_{2max}$ in monozygous compared with dizygous twins (3). A number of studies have also assessed the relationships between specific genetic markers and $\dot{V}O_{2max}$. Dionne and co-workers (4) found that, in the untrained state, three mitochondrial DNA polymorphisms were associated with an increased $\dot{V}O_{2max}$ and one was associated with a decreased $\dot{V}O_{2max}$. The associated allele at these three polymorphic sites was only observed in three or four individuals, and their average $\dot{V}O_{2max}$ was ~10% different from those without the variant. They also found that another mitochondrial DNA allele polymorphism present in three persons was associated with a smaller increase in $\dot{V}O_{2max}$ after exercise training (4). More recently, these authors reported on the effects of an NcoI polymorphism at the muscle-specific creatine kinase gene locus, indicating that $\dot{V}O_{2max}$ was highest in heterozygotes (28 $ml \cdot kg^{-1} \cdot min^{-1}$), lowest in those homozygous for the variant allele (24 $ml \cdot kg^{-1} \cdot min^{-1}$), and intermediate in those homozygous for the common (wild type) allele (26 $ml \cdot kg^{-1} \cdot min^{-1}$) (12). This relationship was evident at baseline in parents but not in their adult offspring. In addition, parents and offspring with at least one wild-type allele increased their $\dot{V}O_{2max}$ more after exercise training, accounting for 9–10% of the variation of change in $\dot{V}O_{2max}$ after exercise training. However, they also reported that these genotypes had the same distribution in elite endurance-trained male athletes and their sedentary peers (13).

Recently, Trent et al. (19) reported that Australian Olympic rowers had an excess of ACE I alleles and the ACE II genotype, in comparison to a population of normal healthy subjects. Because performance in elite rowing events is closely associated with $\dot{V}O_{2max}$ (5, 6, 17), these data are consistent with the present results showing a higher $\dot{V}O_{2max}$ in ACE II genotype carriers. Having the ACE genotype that results in a 3–6 $ml \cdot kg^{-1} \cdot min^{-1}$ higher $\dot{V}O_{2max}$ would clearly be a benefit at an elite level of competition in events where $\dot{V}O_{2max}$ is one of the primary determinants of performance. This is evident in our postmenopausal women athletes where both 5-km and 10-km race times tended to be substantially faster in the ACE II than the DD women [5-km: II 22.7 ± 0.1, ID 24.8 ± 3.1, and DD 28.5 ± 2.8 min (P = 0.098); 10-km: II 51.8 ± 6.7, ID 52.0 ± 5.3, and DD 56.4 ± 2.7 min (P = not significant)].

Our data contrast with the recent findings of Montgomery et al. (10). They showed substantial differences in the physiological LV hypertrophy resulting from military basic training in young men with different ACE genotypes, wherein basic training increased LV mass 2.0, 38.5, and 42.3 g in the ACE II, ID, and DD men, respectively. Because the ACE gene is involved in regulating vascular tone, our finding that the ACE II genotype group has a wider a-vDO_2 suggests a greater release of peripheral vascular tone with attendant greater increases in capillary perfusion and red cell transit time in the ACE II than in the ID and DD genotype groups. One would expect that peripheral vascular resistance would thus be lower in the II genotype, which our data did not show, but some of our blood pressure estimates at maximal exercise were actually measured in early recovery, and arterial and right heart catheters were not used. Assuming that our data and those of Montgomery et al. are true, and that ACE genes serve similar functions in postmenopausal women and young men, the simplest explanation is that there is a better matching of cardiac to peripheral determinants of $\dot{V}O_{2max}$ in the ACE II than in the ID and DD genotype groups. Such a mechanism, integrating cardiovascular biology, would explain our finding of a wider a-vDO_2 in the ACE II genotype group and the finding by Montgomery et al. of physiological LV hypertrophy in only the ACE ID and DD genotype groups. One would then expect to see strong correlations between ACE genotype, a-vDO_2 at maximal exercise, and physiological LV hypertrophy.

From a clinical perspective, it is important to note that both low $\dot{V}O_{2max}$ and the ACE DD genotype have been associated with heightened CV disease risk and all-cause mortality (2, 14). Blair and co-workers (2) reported that in both men and women, after accounting for age and gender, all-cause and CV disease mortality were substantially lower in those with higher levels of CV fitness, indexed as $\dot{V}O_{2max}$. In fact, it appeared that differences in $\dot{V}O_{2max}$ similar to those observed between the homozygous groups in the present study could reduce all-cause mortality by ~40%. Interestingly, a recent meta-analysis indicated that ACE DD genotype carriers were at 36% greater risk of having a myocardial infarction than were ACE II carriers (14). Thus it is possible that one mechanism whereby ACE genotype affects CV disease risk may be via its impact on the peripheral and central factors determining $\dot{V}O_{2max}$.

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