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Angiogenin gene-race interaction for resting and exercise BP phenotypes: the HERITAGE Family Study

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Rivera, Miguel A., Marcos Echegaray, Tuomo Rankinen, Louis Pérusse, Treva Rice, Jacques Gagnon, Arthur S. Leon, James S. Skinner, Jack H. Wilmore, D. C. Rao, and Claude Bouchard. Angiogenin gene-race interaction for resting and exercise BP phenotypes: the HERITAGE Family Study. *J Appl Physiol* 90: 1232–1238, 2001.—We examined the association between an angiogenin gene polymorphism and blood pressure (BP) at rest and in response to acute exercise before and after a 20-wk endurance-training program. Subjects were 737 normotensive and borderline hypertensive subjects (257 black and 480 white). The polymorphism was detected by PCR and digestion with *Ava*II, yielding an allele of 253 bp or a rare allele of 194 + 59 bp. Resting and exercise [50 W; 60, 80, and 100% of maximal O_2 consumption ($\dot{V}O_{2\,max}$)] systolic (SBP) and diastolic BP were determined before and after training. Among blacks, adjusted SBP in the sedentary state was significantly lower in carriers of the rare allele at rest and exercise intensities of 60, 80, and 100% of $\dot{V}O_{2\,max}$. In the trained state, carriers of the rare allele had a significantly ($P < 0.05$) lower SBP than did noncarriers at rest and at 80 and 100% of $\dot{V}O_{2\,max}$. The genotypic effect observed among blacks was not evident among whites. Furthermore, change in BP (after − before) was not significantly associated with the genotype. In conclusion, the angiogenin gene *Ava*II polymorphism is associated with a lower SBP at rest and in response to acute high-intensity exercise in blacks but not in whites.

genetics; *Ava*II; African Americans; acute exercise; endurance exercise

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THE REGULATION OF BLOOD PRESSURE (BP) is influenced by several environmental and genetic factors (5). In North America, marked differences between individuals of African and European descent have been noted in the prevalence of hypertension and pathophysiological conditions related to it (7). Incidence of hypertension among those of African descent is at least twice that of those of European descent for nearly every age- and gender-matched group (6). Using the candidate gene approach, molecular studies have identified several genes influencing BP dynamics (5, 16). However, few data are available regarding the molecular mechanisms underlying BP dynamics in acute or chronic response to exercise. One of the main aims of the HERITAGE Family Study is to perform association and linkage studies between a panel of candidate genes and their possible relation to cardiovascular and metabolic responses to aerobic exercise training (4).

Chromosomal regions showing suggestive linkages with systolic BP (SBP) at rest and in acute response to exercise in the sedentary state as well as its adaptation to endurance training were observed in a recent genome-wide scan in the HERITAGE Family Study (unpublished observations). Among these chromosomal regions was the one enclosing marker D14S283, which is just 3 Mb upstream from the locus of a 14-kDa plasma protein known as angiogenin (ANG). ANG is a very effective inducer of neovascularization and has a high degree of homology with the primary sequence of the RNase A superfamily (22). In fact, it has a distinct, although weak, RNase activity (19). The gene encoding human ANG is located on *chromosome 14*, *region q11* (26). This gene extends over 4,688 bp and lacks introns (10). Messenger RNA for ANG is expressed in a wide range of tumoral and normal human tissues (15), and the protein is present in plasma at concentrations of 250–360 μg/l (20).

The development of vascular networks, angiogenesis, is a key factor that influences individual variability

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in peripheral resistance and BP. It has been demonstrated that differences in capillarization are associated with inherited predisposition for BP abnormalities (12). Along these lines, skin and muscle capillary densities have been shown to be significantly lower in hypertensive subjects compared with normotensive controls (2, 8). This suggests that there are genetic mechanisms underlying angiogenesis that could reflect in BP control.

Because of its constant presence in plasma, it has been suggested that ANG may have other functions besides that of angiogenesis. For example, ANG has been suggested to be part of the host-defense system because of its activity as a tRNase (18). In addition, it has been demonstrated that ANG can promote the secretion of PGI_2 (prostacyclin), a known vasodilator (3). Therefore, ANG could be involved in the regulation of BP, either by affecting the body's capillary network (vascularization) or indirectly by stimulating the release of a vasodilating agent. Hence, it seems to be a reasonable candidate gene to investigate in relation to BP dynamics. The present study examined the hypothesis of an association between an ANG gene polymorphism and BP at rest and in response to acute exercise in the sedentary state, as well as its adaptation [change (Δ)] to the endurance-training program of the HERITAGE Family Study (4).

METHODS

Subjects. The aims, design, and measurement protocol of the HERITAGE Family Study have been described (4). The present study is based on data from 737 (257 blacks and 480 whites) normotensive and borderline hypertensive individuals. Subjects met a series of inclusion criteria including SBP <160 mmHg and diastolic BP (DBP) ≤99 mmHg. The study protocol was previously approved by each of the Institutional Review Boards of the HERITAGE Family Study research consortium. Written informed consent was obtained from each participant. Mean age and physical characteristics of the subjects are presented in Table 1.

BP and exercise test methodology. BP measures were taken in the morning with the use of the Colin STBP-780 automated BP unit (San Antonio, TX) as described earlier (4). Proper cuff size (child, regular adult, or large adult) was determined by using recent guidelines (11). Subjects were seated in a reclining chair in a semirecumbent position. The laboratory was quiet, with little light and a room temperature between 23 and 26°C. After a rest period of at least 5 min, four BP readings were taken at 2-min intervals. The retained BP was the mean of three valid measurements. Subjects reported to the laboratory on a second day, within ±2 h of the time of the first day, and the same procedures were repeated.

Subjects completed a total of three exercise tests, each on a different day, both before and after training: a maximal test (Max), a submaximal test (Submax), and a Submax to Max test (Submax/Max) (21). All exercise tests were conducted on a cycle ergometer (SensorMedics Ergo-Metrics 800S, Yorba Linda, CA). Subjects completed the initial Max exercise test using a graded exercise test protocol, starting at 50 W for 3 min. The rate of work was then increased by 25 W every 2 min thereafter to the point of exhaustion. With the use of the results of this initial Max test, subjects then performed the Submax test on a second day, exercising at 50 W and 60% of their initial maximal O_2 consumption ($\dot{V}O_{2\,max}$). Subjects exercised for ~12 min at each work rate, with a 4-min period of seated rest between work rates. The Submax/Max exercise test was then performed on a third day, starting with the Submax protocol, i.e., 50 W and 60% of the initial $\dot{V}O_{2\,max}$, and progressing to 80% of $\dot{V}O_{2\,max}$ for 3 min and maximal level of exertion ($\dot{V}O_{2\,max}$).

During the Submax and Submax/Max tests, BP values were obtained at 50 W and at 60% of the initial $\dot{V}O_{2\,max}$, whereas peak BP was obtained at the very end of the Max and Submax/Max tests. The values used in this paper are the means of the results obtained during the two Submax tests (Submax and Submax/Max) and for the two Max tests (Submax/Max and Max) before and after the training program. BP at 80% of initial $\dot{V}O_{2\,max}$ was obtained during the Submax/Max test. For all exercise tests, O_2 consumption, CO_2 production, expiratory minute ventilation, and the respiratory exchange ratio were determined every 20 s and reported as a rolling average of the three most recent 20-s values using a SensorMedics 2900 metabolic measurement cart. $\dot{V}O_{2\,max}$ was defined as the peak value obtained during the test. Heart rate was determined by electrocardiogram and the Colin STBP-780 instrument, and values were recorded during the last 15 s of each stage of the Max test and once steady state had been achieved at each of the submaximal work rates during the Submax/Max tests. Further details concerning BP and exercise test methodology can be obtained from recent publications (21, 27).

Endurance exercise training program. Participants trained under supervision were required to complete 60 training sessions within 21 wk. They could not exercise for more than one session/day, more than four sessions/week, or less than one session/week. In addition, they could not get ahead by more than two sessions or fall behind by more than two sessions. Participants who knew they might miss a few sessions were encouraged to train four times/week for 2 wk to build up a reserve. Program adherence was monitored several times per week. Participants were contacted when they appeared to be falling behind, and a plan was then developed to bring them back on schedule as soon as possible. Only subjects who completed at least 57 sessions (>95% of target) were kept for the present study.

Briefly, subjects exercised following a standardized protocol that required the use of a cycle ergometer (Universal Aerobicycle IV, Cedar Rapids, IA) in the sitting position. The cycle ergometer was connected to a computer system (Universal Mednet, Cedar Rapids, IA) that adjusted the power output of the ergometers to maintain constant training heart rates. During the initial 2 wk, subjects trained at a heart rate

Table 1. *Subjects' characteristics*

Group	n	Age, yr	Mass, kg	BMI, kg/m^2	SBP, mmHg	DBP, mmHg
Blacks	257	34.1 ± 11.8	77.8 ± 17.5	28.0 ± 5.9	123.2 ± 12.2	72.8 ± 8.4
Whites	480	35.9 ± 14.6	75.6 ± 17.4	25.9 ± 5.0	116.4 ± 11.1	66.1 ± 8.4

Values are means ± SD. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

associated with 55% of each subject's $\dot{V}O_{2\,max}$ for 30 min/session. This was gradually increased to 50 min by the end of the 14th wk at the heart rate associated with 75% of $\dot{V}O_{2\,max}$. These levels of intensity and duration were maintained through the remaining 6 wk. Further details concerning the training program can be found in previous publications (21, 27).

Genotype determinations. DNA was extracted from lymphoblastoid cell lines after digestion by proteinase K and purification with phenol-chloroform. The PCR amplification targeted a region (1,944–2,196 bp) in codon 86, which includes the polymorphic site at 2,138 bp (T → G). The primers were as follows: 5′-GAT-GAC-AGA-TAC-TGT-GAA-AGC-ATC-3′ (sense) and 5′-CAA-CAA-CAA-CGT-TTC-TGA-ACC-C-3′ (antisense). A product of 253 bp was obtained. The PCR reaction mixture and amplification protocols have been described previously (14).

The PCR product was digested with 10 units of *Ava*II. Restriction digest conditions were those recommended by the enzyme manufacturer (New England Biolabs, Mississauga, Ontario). The resulting fragments were separated by horizontal electrophoresis on 4% agarose gels. Each gel was run for 60 min at 150 mA while refrigerated at 10°C, stained with ethidium bromide, and photographed under ultraviolet

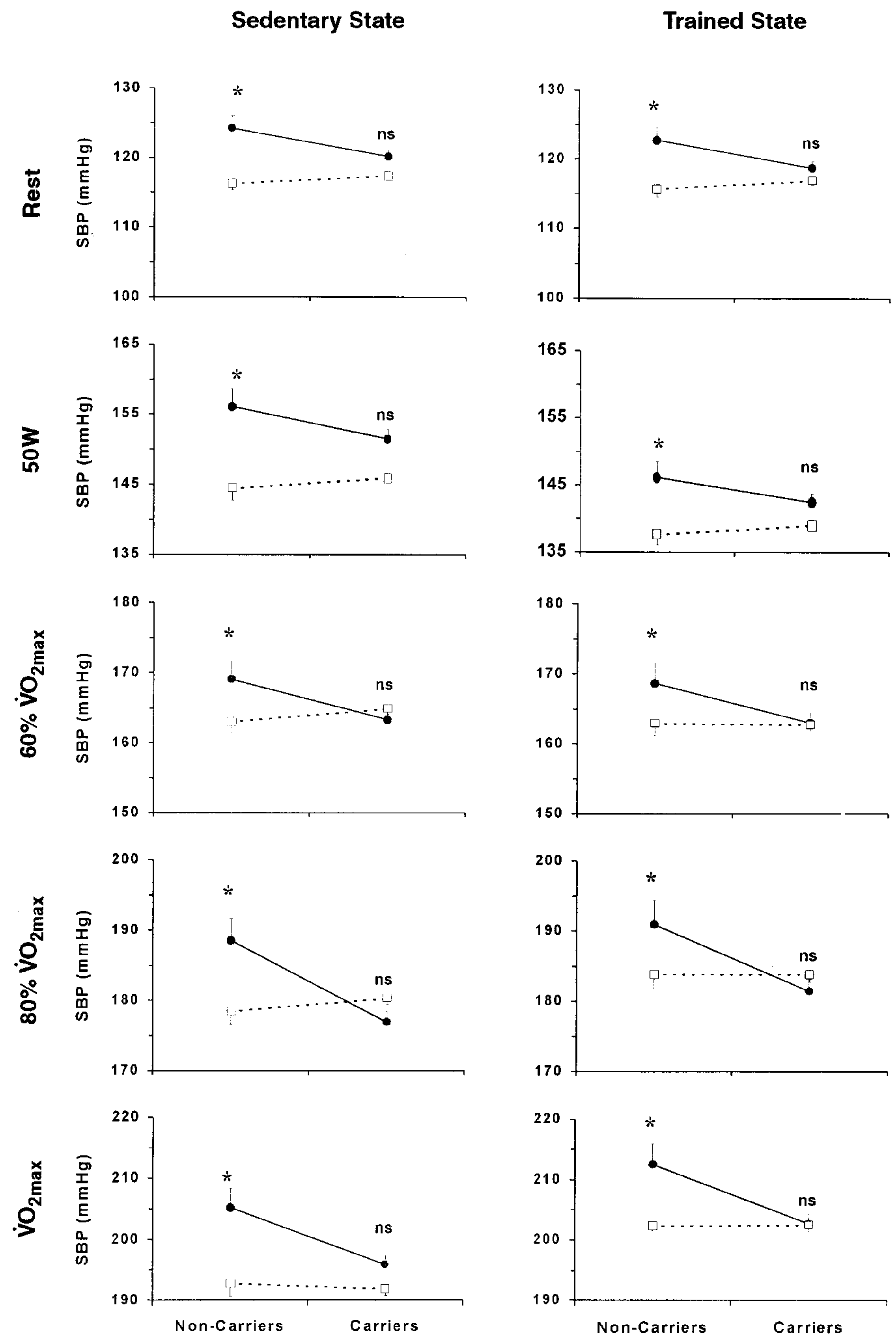

Fig. 1. Race angiogenin *Ava*II genotype interactions for sedentary and trained state systolic blood pressure (SBP) at rest, 50 W, and 60, 80, and 100% of maximal O_2 consumption ($\dot{V}O_{2max}$) in black (●) and white (□) subjects of the HERITAGE Family Study. Carriers, G allele homozygotes (GG) and heterozygotes (GT); noncarriers, TT homozygotes. Values are means ± SE; *Significant difference compared with white noncarriers, $P < 0.05$; ns, nonsignificant compared with white carriers.

transmitted lights. The ΦX174 DNA, digested with *Hae*III, was used as length marker to estimate the size of the digested DNA fragments. The allele without the mutation (wild type) was designated as the T allele, whereas the allele with the cutting site (194 + 59 bp) was designated as the G allele.

Statistical analysis. A χ^2 test was used to examine gender differences in allele and genotype frequencies and to determine whether the observed genotype frequencies were in Hardy-Weinberg equilibrium. Associations between BP phenotypes and the genetic marker were tested with analysis of covariance by using the general linear model procedure of the SAS package (SAS Institute, Cary, NC) for personal computer (version 6.08) (17). Baseline phenotypes were adjusted for age, gender, and body mass index (BMI), whereas posttraining values were adjusted for age, gender, and posttraining BMI. Training response (ΔBP = pretraining − posttraining) was adjusted for age, gender, baseline BMI, and baseline value of the phenotypes. Possible generation-by-genotype interaction effects were tested by introducing an interaction term in the general linear model in addition to the genotype and generation main effects. If the interaction term was significant, association analyses were performed separately in parents and offspring. In addition to the fully adjusted models, analyses were also performed without adjustment, by adjusting for each of the covariates separately and by using various combinations of covariates. The results of all of these analyses were globally identical to those of the full model, and, therefore, only the data from the full models are reported in the present study.

All of the family members were included in the analysis. It is commonly believed that the relatedness of the subjects in family study cohorts may cause problems in association analyses. However, a recent simulation study (M. A. Province, T. Rice, and D. C. Rao, unpublished observations) suggests that this is not the case. The problem is that within-person effects violate the basic independent, identically distributed errors' assumption of classical statistical theory. Familial clusters of residuals are statistically independent, but the model errors for individuals within the same family are often dependent. In the Province et al. (M. A. Province, T. Rice, and D. C. Rao, unpublished observations) simulation study, the data were analyzed by four methods. The least squares method used in the present study was one of them; the other three methods treated dependencies in different ways. Two major findings are pertinent here. First, failure to incorporate dependencies did not induce any bias. Second, for moderate familial correlations as seen in most family studies (including the present one), ignoring the dependencies by using ANOVA performed quite well. The only negative impact was a small reduction in power. The standard errors are slightly larger, but type I error was unaffected. Given this, we do not believe that the dependencies or relatedness of the subjects in families causes any real problems in this type of analysis.

RESULTS

The χ^2 analysis showed that neither allelic nor genotype frequencies were significantly different between genders in blacks or whites, respectively. In addition, no significant differences in allelic (0.93 and 0.07 vs. 0.89 and 0.11 for black men and women vs. white; $P = 0.34$) or genotype frequencies ($P = 0.36$) existed between races. The observed genotypic frequencies for both races were in Hardy-Weinberg equilibrium. Because of the low frequency of homozygotes for the rare G allele ($n = 1$ in blacks; $n = 3$ in whites) for each race, their data were pooled with those of heterozygotes (T/G). Those two groups were designated as "carriers," whereas homozygotes for the T allele were designated as "noncarriers." Significant race-genotype interactions ($P < 0.05$) were found at rest and at all exercise intensities for sedentary-state SBP and at rest, 50 W, and 80 and 100% $\dot{V}O_{2\,max}$ in the trained state (Fig. 1). Because of these findings, data for black and white subjects were analyzed separately.

Figure 2 shows the sedentary-state SBP for carriers and noncarriers of the rare G allele for black subjects. Among this group of subjects, carriers of the rare allele had a significantly ($P < 0.05$) lower sedentary-state SBP than did noncarriers at rest and at 60, 80, and 100% of $\dot{V}O_{2\,max}$. In the trained state (Table 2), black carriers of the rare allele had a significantly ($P < 0.05$) lower SBP than did noncarriers at rest and at 80 and 100% of $\dot{V}O_{2\,max}$. Although there were no significant associations at 50 W, significant gene-race interactions were present in both the sedentary and trained state at this intensity. This is illustrated in Fig. 1, where the lines corresponding to the genotype effect in blacks and whites depart from parallelism.

However, none of the significant genotypic effects observed in blacks was evident in whites. Among white subjects, a significant ($P = 0.04$) difference between carriers and noncarriers was evident only for sedentary-state DBP at 50 W (Table 3). In addition, the response (ΔBP) to the 20-wk endurance-training program was not significantly associated with genotype in any group (data not shown).

Comparison of white and black noncarriers in the sedentary and trained state showed that the former had significantly ($P < 0.05$) lower SBP and DBP at rest and at all exercise intensities. However, among carri-

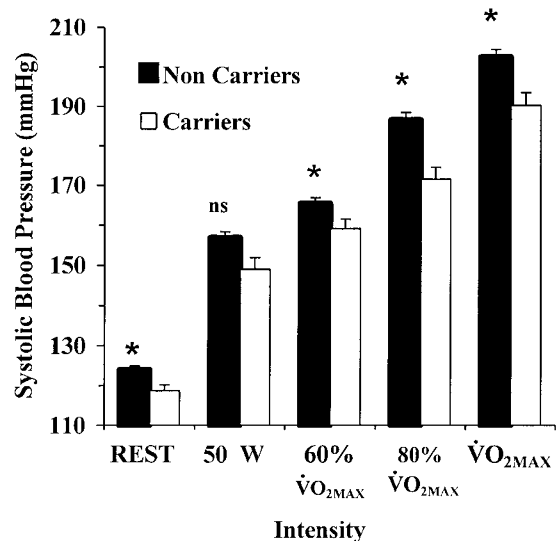

Fig. 2. Sedentary state (before training) SBP in carriers ($n = 49$) and noncarriers ($n = 208$) of the angiogenin gene *Ava*II G allele at rest, 50 W, and 60 and 80% of $\dot{V}O_{2\,max}$, as well as $\dot{V}O_{2\,max}$, in normotensive and borderline hypertensive blacks ($n = 257$) of the HERITAGE Family Study. Values are means ± SE. *Significant difference vs. carriers, $P < 0.05$.

Table 2. *Trained-state resting and exercise blood pressure by angiogenin gene AvaII polymorphism (codon 86) carrier status in black and white subjects of the HERITAGE Family Study*

	Blacks		Whites		
Phenotype	Carriers (n = 49)	Noncarriers (n = 208)	Carriers (n = 98)	Noncarriers (n = 382)	Race-by-Genotype Interaction, P value
SBP					
Resting	118.8 ± 1.8*	122.8 ± 0.9	116.9 ± 1.1	115.7 ± 0.5	<0.01
50 W	142.5 ± 2.4	146.1 ± 1.2	139.0 ± 1.5	137.6 ± 0.7	<0.02
60% $\dot{V}O_{2\,max}$	163.1 ± 2.9	168.7 ± 1.4	162.8 ± 1.7	162.9 ± 0.9	<0.07
80% $\dot{V}O_{2\,max}$	181.4 ± 3.4*	191.0 ± 1.7	183.8 ± 2.0	183.8 ± 1.0	<0.03
$\dot{V}O_{2\,max}$	202.7 ± 3.4*	212.6 ± 1.7	202.5 ± 2.3	202.4 ± 1.1	<0.02
DBP					
Resting	70.9 ± 1.3	72.3 ± 0.6	66.9 ± 0.8	65.2 ± 0.4	<0.06
50 W	72.4 ± 1.4	74.3 ± 0.6	68.6 ± 0.8	67.7 ± 0.4	<0.09
60% $\dot{V}O_{2\,max}$	72.5 ± 1.4	75.3 ± 0.7	69.4 ± 0.9	67.9 ± 0.4	<0.01
80% $\dot{V}O_{2\,max}$	78.8 ± 1.7	79.8 ± 0.8	73.5 ± 1.1	72.8 ± 0.6	<0.49
$\dot{V}O_{2\,max}$	81.9 ± 1.9	86.0 ± 1.0	79.9 ± 1.2	78.1 ± 0.6	<0.02

Values are means ± SE. $\dot{V}O_{2\,max}$, maximal O_2 consumption. *$P < 0.05$ vs. black noncarriers.

ers there was no significant difference in sedentary- or trained-state SBP at any of the exercise intensities tested. Nonetheless, in those subjects, significant differences in DBP persisted.

DISCUSSION

The existence of interactions between racial background and BP phenotype has been acknowledged for some time (1). However, information on how these racial differences relate to exercise and exercise training has been scarce. The present study utilized the candidate gene approach to investigate the association between a polymorphism in the human ANG gene and BP phenotypes at rest and at different intensities of exercise before and after a carefully standardized and monitored endurance-training program.

The main finding of this study was that, among black subjects, the presence of the *Ava*II rare G allele was associated with a lower SBP at rest and at exercise intensities of 60, 80, and 100% of $\dot{V}O_{2\,max}$ compared with the noncarriers. The genotypic effect was present in both the sedentary state and after a 20-wk cardiorespiratory endurance-training program. To our knowledge, the *Ava*II marker is the only restriction fragment-length polymorphism reported so far for the ANG gene. The present marker is a silent transversion (T → G) present at the third position in codon +86 and does not alter the encoded amino acid (26). Yet the *Ava*II restriction fragment-length polymorphism could be in linkage disequilibrium with more meaningful mutations in the ANG gene (or perhaps another gene), and the results may have implications far beyond the specific polymorphism considered here.

It is noteworthy that no genotypic effect was observed among white subjects. Furthermore, black noncarriers had significantly higher sedentary-state and trained-state SBP than did whites at rest and during exercise. However, when mean SBP of carriers was compared, these racial differences were no longer detectable. Therefore, the mutation is associated in blacks with a lower sedentary-state SBP, which results in a SBP similar to that of whites.

ANG is a potent angiogenic agent in biological assays and is synthesized in normal and tumoral tissues (23).

Table 3. *Sedentary-state resting and exercise blood pressure by angiogenin gene AvaII polymorphism (codon 86) carrier status in black and white subjects of the HERITAGE Family Study*

	Blacks		Whites		
Phenotype	Carriers (n = 49)	Noncarriers (n = 208)	Carriers (n = 98)	Noncarriers (n = 382)	Race-by-Genotype Interaction, P value
SBP					
Resting	120.2 ± 1.7*	124.3 ± 0.8	117.4 ± 1.0	116.3 ± 0.5	<0.001
50 W	151.5 ± 2.6	156.1 ± 1.3	145.9 ± 1.7	144.4 ± 0.8	<0.01
60% $\dot{V}O_{2\,max}$	163.4 ± 2.6*	169.1 ± 1.3	164.9 ± 1.7	163.1 ± 0.8	<0.007
80% $\dot{V}O_{2\,max}$	176.9 ± 3.1*	188.6 ± 1.6	180.3 ± 1.9	178.5 ± 0.9	<0.001
$\dot{V}O_{2\,max}$	195.9 ± 3.1*	205.3 ± 1.6	191.9 ± 2.1	192.8 ± 1.1	<0.03
DBP					
Resting	70.9 ± 1.1	73.2 ± 0.6	66.9 ± 0.7	66.0 ± 0.4	<0.03
50 W	78.4 ± 1.4	79.8 ± 0.7	73.1 ± 0.9†	70.8 ± 0.5	<0.03
60% $\dot{V}O_{2\,max}$	78.9 ± 1.3	81.3 ± 0.7	73.9 ± 0.9	72.3 ± 0.5	<0.03
80% $\dot{V}O_{2\,max}$	82.8 ± 1.8	84.3 ± 0.9	76.0 ± 1.1	75.7 ± 0.6	<0.42
$\dot{V}O_{2\,max}$	88.1 ± 1.8	89.6 ± 0.9	82.8 ± 1.3	81.4 ± 0.6	<0.18

Values are means ± SE. *$P < 0.05$ vs. black noncarriers; †$P < 0.05$ vs. white noncarriers.

In this context, it is possible that, among black subjects, the rare allele is a marker of greater vascularization of skin, cardiac, and/or skeletal muscle. Because the microcirculation is a key site of vascular resistance control, greater vascularization could translate into a greater capacity to handle increased peripheral blood flow, and, therefore, a lower BP at rest and in response to exercise may be expected. This latter assumption is supported by the significant differences in SBP between carriers and noncarriers observed not only through moderate-to-maximal exercise, but also at rest when vasodilating mechanisms are not necessarily active.

Although increases in muscle capillary density are known to occur in response to endurance exercise training (9), in the present study there was no significant association between ANG *Ava*II genotype and ΔBP. The fact that significant differences in SBP between ANG genotypes were present, both in the sedentary and trained state, seems to suggest that this is a marker for vascularization as an inherited and lifelong characteristic and may not necessarily interact with training. In agreement with this, it has been observed that defective angiogenesis is associated with inherited propensity for the development of hypertension (12).

On the other hand, ANG could affect other mechanisms related to BP regulation. For instance, it has been demonstrated that ANG can promote the secretion of PGI_2 from endothelial cells (3). PGI_2 is known to exert a relaxant effect on coronary, pulmonary, cerebral, mesenteric, and renal vascular tone, thus lowering BP. Interestingly, it has been shown that infusion of PGI_2 alters BP differentially, depending on the dose. The lowering effect is seen predominantly on SBP and to a lesser degree on DBP when doses of 20 $ng \cdot kg^{-1} \cdot min^{-1}$ or more are infused (24). Thus it may be speculated that significant differences seen here in SBP but not in DBP could be the result of the vasodilatory capacity of PGI_2 at high concentrations. Although PGI_2 has been observed to increase in response to acute strenuous exercise, no significant differences in circulating concentrations of PGI_2 existed between endurance athletes and sedentary controls (25). Thus it has been suggested that the elevation in the concentration of PGI_2 during acute strenuous exercise is a normal physiological response and does not necessarily change with training. This is consistent with the lack of difference in ΔBP between ANG genotypes in the present study.

In summary, the results demonstrate that, among blacks, a significant association exists between a polymorphism of the ANG gene and SBP at rest and during exercise in both the sedentary and trained states. Carriers of the rare G allele showed significantly lower SBP at rest and during exercise intensities of 60, 80, and 100% of $\dot{V}O_{2\,max}$. The genotype effect was not evident in the SBP response (Δ) to the endurance-training program in any of the groups. Furthermore, none of the genotype effects observed in blacks was detected among white subjects. The significant association between the ANG locus and the SBP phenotypes indicates that the ANG gene, or a gene in linkage disequilibrium with it, may be responsible for the observed differences. Further research is necessary to establish the true nature of this association. Differences in skin, cardiac, or muscle vascularization or in PGI_2-mediated vasodilation should be considered as possible mediators.

In conclusion, the observed interaction between race and the ANG *Ava*II marker partially explains racial differences in BP at rest and in acute response to exercise in the sedentary and trained states. The significant association between genotype and BP phenotypes provides further insight into the genetic control of BP at rest and during exercise.

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