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Familial Aggregation of Exercise Heart Rate and Blood Pressure in Response to 20 Weeks of Endurance Training: The HERITAGE Family Study

Abstract

Changes of heart rate (HR) and blood pressure (BP) relative to baseline levels in response to an extended period of endurance training are indices of cardiovascular adaptability. Familial influences were investigated for HR and BP at work rates of 50 W and 60% of the maximal oxygen uptake ($\dot{V}O_2$max) in response to 20 weeks of endurance training. A total of 481 participants from 99 sedentary White nuclear families in the HERITAGE Family Study (HERITAGE) were analyzed using a familial correlation model. Each of these training response phenotypes was adjusted for the effects of age, BMI, cigarette smoking, baseline $\dot{V}O_2$max, and its baseline values in fathers, mothers, sons and daughters, respectively. We found that maximal heritabilities reached 34% and 29% for HR training responses at 50 W and 60% of $\dot{V}O_2$max, respectively. The heritability was 22% for systolic BP (SBP) training response at 50 W, but negligible at 60% of $\dot{V}O_2$max. No significant heritabilities were found for diastolic BP (DBP) training responses at either 50 W or 60% of $\dot{V}O_2$max. Familial influences for exercise HR and BP training responses were also assessed in a total of 257 participants from 113 Black family units in HERITAGE. However, there was no significant familial resemblance, which may be attributable to the small sample size. In conclusion, HR and SBP training responses during submaximal exercise in Whites were influenced by a modest, but significant, familial component. These observations are therefore in contrast to substantial familial effects (heritability estimates of about 50%) previously reported for these variables measured at baseline.

Key words
Maximal heritability · genetics · shared environments

Introduction

Levels of heart rate (HR) and systolic blood pressure (SBP) increase in response to acute exercise. An exaggerated acute BP response to exercise (usually maximal exercise) may be a predictor of future essential hypertension [1–4]. In contrast, it has been reported that HR and BP levels decrease in response to a period of regular endurance training [5]. Recently, modest reductions in resting HR and BP levels and substantial reductions in exercise HR and BP levels in response to a 20-week endurance training program have been observed in the HERITAGE Family Study (HERITAGE) [6]. Regular exercise training aimed at bringing about HR and BP level reductions is physiologically and clinically important, and is recommended to treat individuals with mild to moderate elevations in BP. Both genetic and environmental factors may influence changes of HR and BP levels during exercise in response to regular endurance training, although such factors have not been adequately studied.

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Familial resemblance for resting HR, SBP, and diastolic BP (DBP) has been well documented in previous studies, with some genes having a relatively large effect [7 – 13]. More recently, we found a significant familial component in White families in HERITAGE for HR (heritability, $h^2 = 34\%$), SBP ($h^2 = 51\%$), and DBP ($h^2 = 42\%$), all at rest [12 – 13]. The maximal heritability reached 26% for the training response in resting HR [14]. Genetic influences for these variables in response to acute exercise have also been investigated. During submaximal exercise at 50 Watts (W), the estimates for HR, SBP, and DBP reached 59%, 45% and 55%, respectively [15]. Heritabilities were 46% for HR, 25% for SBP, and 42% for DBP during submaximal exercise at 60% of maximal oxygen uptake ($\dot{V}O_2$max) [15]. A significant genetic component was also found for acute DBP response to exercise in 81 Utah pedigrees [16]. The purpose of the current investigation is to assess familial resemblance for changes in exercise HR and BP levels in response to regular endurance training in HERITAGE.

Material and Methods

Investigation of the genetic influences on risk factors of cardiovascular disease and type 2 diabetes mellitus is one of the major goals of the HERITAGE Family Study [17]. Families were recruited through extensive media publicity and advertisements. Approval was obtained from the Institutional Review Boards (IRB) at each of the four participating clinical centres, and written informed consent was obtained from each participant. Several criteria were used to screen participants. Subjects had to be in good health and able to complete the 20-week endurance exercise training program. They were required to be sedentary at baseline, i. e., not engaged in regular strenuous exercise lasting more than 30 minutes per week, for at least 6 months prior to study entry. Parents had to be 65 years of age or younger, and offspring between 17 – 40 years of age. All subjects had their resting SBP and DBP ≤ 159 and 99 mm Hg, respectively, and BMI < 40 kg/m^2. Several participants with their BMI slightly higher than 40 kg/m^2 were also included in this study with a supervising physician's approval, because they were considered to be 'healthy' and able to complete the required exercise training program. Antihypertensive drug therapy was a cause for exclusion [17]. In the current study, a total of 481 individuals from 99 White families (232 men, 249 women; 4, 19, 57, 17, 2 families with both parents and 1, 2, 3, 4, 5 offspring, respectively) and a total of 257 individuals from 113 Black family units (88 men, 169 women; 53, 42, 12, 1, 1 families with both parents and 1, 2, 3, 4, 5 offspring, respectively) completed the 20-week training program. Participants with incomplete pre-training (before training) and post-training (after training) exercise HR and BP measurements were not included in the analysis. The sample sizes within 4 sex-by-generation groups (fathers, mothers, sons, daughters) for the pre-training and the training responses of HR and BP during submaximal exercise, i. e., at 50 W and 60% $\dot{V}O_2$max, are presented in Table **1a** (Whites) and Table **1b** (Blacks).

Each subject was administered a comprehensive battery of tests prior to the 20-week training program, which included HR and BP measured twice at 50 W and twice at 60% $\dot{V}O_2$max on each of two separate days [6]. Subjects then completed 60 sessions of endurance exercise training (3 sessions per week for 20 weeks) on cycle ergometers that were computer controlled to maintain the subjects' HRs at levels associated with fixed percentages of their $\dot{V}O_2$max [18 – 19]. The training program started at 55% $\dot{V}O_2$max for 30 minutes per session for 14 weeks, and gradually increased to 75% $\dot{V}O_2$max for 50 minutes per session during the last 6 weeks of training. All training sessions were supervised and adherence to the protocol was strictly monitored. The full test battery was administered again after the training program.

HR and BP measurement techniques and exercise test methodology have been explicitly described [6,18]. For HR and BP measurements at rest, subjects reported to the laboratory before 11 : 00 a. m., having restrained from tobacco products and caffeine beverages for at least 2 hours, and having performed no formal exercise in 12 hours. The ambient laboratory temperature was maintained at 24 – 26 °C. Electrodes were attached for electrocardiograph (ECG) monitoring. A blood pressure cuff with an appropriate size was placed on each subject's right arm. Subjects rested for 5 minutes in a comfortable upholstered chair before resting HR was obtained from ECG reading. The resting BP measurements were obtained with the arm supported at the level of the heart using a Colin STBP-780 automated blood pressure monitoring unit (San Antonio, TX) with confirmation of readings made by trained technicians monitoring BP readings with head phones. A series of 4 – 8 HR and BP measurements were taken on each of two separate days before and after the training program. Exercise HR and BP before and after the training program were measured under the same conditions, but testing was not limited to the early morning hours. Exercise HR and BP measurements were obtained on each of the two separate days after subjects reached a steady state during 8 – 12 minutes of pedaling on a cycle ergometer at 50 W and again during 8 – 12 minutes of pedaling at 60% of their initial $\dot{V}O_2$max, with two measurements at each power output. The same protocol was used before and after the training program, but post-training exercise HR and BP measurements were made at 24 hours and 72 hours after the last training session.

Four individual measurements for each of the baseline and post-training HR and BP phenotypes on each of the work rates were averaged. The training response was determined by a simple difference of the averaged values of the post-training and the averaged values of the baseline levels. The baseline exercise HR and BP measurements in general were highly reproducible, with intraclass correlations over 0.80 and coefficients of variation below 9% for repeated measurements [20]. They were therefore measured with good precision, which is necessary for a meaningful interpretation of exercise HR and BP training responses.

Data adjustments were performed within each of the 4 sex-by-generation groups by race in both the mean and the variance using a stepwise multiple regression procedure. Each of the exercise HR and BP training response phenotypes were adjusted for the effects of age, age^2, age^3, cigarette smoking, BMI, baseline $\dot{V}O_2$max, and the baseline values of the phenotype. For each of the regressions, only terms significant at the 5% level were retained. Each of the adjusted phenotypes used in the genetic analysis was finally standardized to zero mean and unit variance, which constituted the analysis variable.

Table **1 a** Means of unadjusted submaximal exercise HR (beats/min) and BP (mmHg) in Whites

Variables	*No.*	*Means Fathers*	*SD*	*No.*	*Means Mothers*	*SD*
Age (years)	93	53.4#	5.5	90	52.1#	5.1
HR:						
50 W, Pre-training	92	105.2*	11.8	89	128.1*	16.4
50 W, Response	92	−8.5*	8.6	89	−14.8*	10.1
60 %, Pre-training	92	128.1#	14.8	89	130.0#	15.3
60 %, Response	92	−5.1	9.7	89	−6.8#	11.2
SBP:						
50 W, Pre-training	91	154.0#	21.7	90	157.7#	25.3
50 W, Response	91	−8.7#	11.2	90	−11.9#	14.5
60 %, Pre-training	93	177.2*,#	19.5	88	159.3*,#	20.0
60 %, Response	93	−2.6	13.1	88	−3.0#	12.8
DBP:						
50 W, Pre-training	92	77.7#	11.3	89	78.4#	9.9
50 W, Response	92	−3.8*	6.7	89	−6.1*,#	6.2
60 %, Pre-training	93	78.8#	11.2	88	78.6#	9.4
60 %, Response	93	−5.6	6.9	88	−5.8#	6.4
		Sons			*Daughters*	
Age (years)	139	25.4#	6.1	159	25.6#	6.4
HR:						
50 W, Pre-training	138	107.0*	11.3	159	127.9*	14.4
50 W, Response	138	−8.7*	8.4	159	−12.5*	10.3
60 %, Pre-training	138	146.7*,#	12.9	159	150.2*,#	14.8
60 %, Response	138	−6.6*	10.2	159	−3.7*,#	10.2
SBP:						
50 W, Pre-training	136	140.5*,#	13.4	154	134.3*,#	12.1
50 W, Response	136	−4.5#	10.1	154	−5.4#	9.2
60 %, Pre-training	137	172.4*,#	16.0	157	148.5*,#	14.4
60 %, Response	137	−0.1	13.9	157	2.0#	10.1
DBP:						
50 W, Pre-training	136	68.3*,#	9.6	154	65.2*,#	8.6
50 W, Response	136	−2.5	6.5	154	−2.6#	6.7
60 %, Pre-training	137	69.5*,#	9.8	159	66.5*,#	9.8
60 %, Response	137	−4.2	7.9	159	−3.4#	7.1

* significant ($p < 0.05$) mean differences for father-mother or son-daughter (within generation) comparisons; # significant ($p < 0.05$) mean differences for father-son or mother-daughter (within sex) comparisons

A sex-specific model was used to estimate familial correlations for submaximal exercise HR and BP training responses. The computer program SEGPATH was employed to fit the sex-specific familial correlation model directly to the family data using the maximum likelihood method [21]. The general model was based on the 4 sex-by-generation groups, which gives rise to 1 spouse (*fm*), 4 parent-offspring (*fs, fd, ms, md*) and 3 sibling (*ss, dd, sd*) correlations. The likelihood ratio test (LRT) and the Akaike Information Criterion (AIC) were used to compare models [22]. The presence of sibling, parent-offspring and spouse correlations, along with sex and generation differences in the correlations were assessed by tests of hypotheses. By combining the non-rejected models into a single test, the most parsimonious hypothesis was chosen with the smallest AIC value. The maximal heritability includes both polygenic and shared environmental sources of variance adjusted for the degree of spouse resemblance. It was computed using the equation $(r_{sibling}+r_{parent\text{-}offspring}) \times (1 + r_{spouse}) / [(1 + r_{spouse}) + 2r_{spouse}r_{parent\text{-}offspring}]$ [23].

Results

Means and SD of unadjusted HR and BP training responses, as well as their baseline levels during submaximal exercise, are given in Table **1a** for Whites and Table **1b** for Blacks. In Whites, the percentages of variance accounted for by baseline exercise HR, BMI, age, age^2, age^3 were 13 % to 54 % in exercise HR training responses. Whereas baseline exercise SBP, BMI, $\dot{V}O_2$max, age^3 and cigarette smoking accounted for 6 % to 40 % of the variance in exercise SBP training responses, the percentages accounted for by baseline exercise DBP, BMI and age ranged from 18 % to 35 % in exercise DBP training responses. In Blacks during submaximal exercise at both the work rates, baseline HR, age, age^2, BMI and baseline $\dot{V}O_2$max accounted for 29 % to 70 % of the variance in HR training responses, baseline SBP and baseline $\dot{V}O_2$max accounted for up to 51 % of the variance in SBP training responses, whereas baseline DBP and BMI accounted for up to 50 % of the variance in DBP training responses.

Table **1 b** Means of unadjusted submaximal exercise HR (beats/min) and BP (mmHg) in Blacks

Variables	*No.*	*Means Fathers*	*SD*	*No.*	*Means Mothers*	*SD*
Age (years)	24	50.9*,#	7.4	50	47.0*,#	6.7
HR:						
50 W, Pre-training	24	113.4*	15.8	48	136.2*	17.7
50 W, Response	24	–11.3	12.4	48	–15.0	9.9
60 %, Pre-training	24	127.1#	17.9	49	128.0#	15.4
60 %, Response	24	–4.9	15.1	49	–0.3	10.8
SBP:						
50 W, Pre-training	24	171.8#	19.1	49	172.1#	23.8
50 W, Response	24	–16.2#	12.9	49	–16.0#	12.1
60 %, Pre-training	24	185.1*	18.0	50	162.1*,#	19.9
60 %, Response	24	–5.2	16.9	50	2.2	16.7
DBP:						
50 W, Pre-training	24	88.6#	7.7	49	88.6#	11.0
50 W, Response	24	–7.6#	6.3	49	–7.5	6.3
60 %, Pre-training	24	89.7#	6.4	50	88.1#	9.6
60 %, Response	24	–7.0	6.0	50	–7.1	6.2
		Sons			*Daughters*	
Age (years)	64	28.6#	7.2	119	28.3#	7.6
HR:						
50 W, Pre-training	64	107.2*	9.8	118	134.7*	16.6
50 W, Response	64	–7.5*	7.9	118	–13.4*	10.8
60 %, Pre-training	64	135.8*,#	11.1	119	140.7*,#	14.9
60 %, Response	64	–2.8	10.5	119	–2.3	8.9
SBP:						
50 W, Pre-training	64	147.8#	13.2	114	148.1#	16.5
50 W, Response	64	–5.4*,#	11.1	114	–9.6*,#	10.8
60 %, Pre-training	64	175.6*	21.1	116	154.3*,#	16.5
60 %, Response	64	1.2	16.7	116	–1.1	12.2
DBP:						
50 W, Pre-training	63	76.8#	9.9	115	75.7#	9.6
50 W, Response	63	–4.5#	6.2	115	–5.8	7.4
60 %, Pre-training	64	78.4#	11.3	117	77.5#	9.3
60 %, Response	64	–5.0	7.5	117	–7.1	7.0

* significant ($p < 0.05$) mean differences for father-mother or son-daughter (within generation) comparisons; # significant ($p < 0.05$) mean differences for father-son or mother-daughter (within sex) comparisons

Familial correlation model-fitting results for exercise HR and BP training responses in Whites are presented in Table **2**. For HR training response at 50 W, model 2 was rejected suggesting the presence of a significant familial component. Models 3 through 5 were not rejected, which indicated the absence of sex and generation differences in the familial correlations. Models 6 through 8 were all rejected, which suggested significant sibling, parent-offspring, and spouse correlations. Finally, a model (9) positing a single correlation, regardless of genetic relationship, was not rejected; and it was the most parsimonious according to the AIC (9.68). For HR training response at 60 % $\dot{V}O_2$max, the familial correlations exhibited no sex and generation differences. Whereas both sibling and spouse correlations were evident, parent-offspring correlations were of borderline significance (model 7, $p = 0.066$). According to the AIC (7.32), a single correlation for all first-degree relatives was the most parsimonious.

For SBP training response at 50 W, the familial component was significant with no sex and generation differences in the correlations. No significant parent-offspring and spouse correlations were found when allowing for sibling correlations. A single correlation hypothesis was tested with (model 9) and without (model 10) spouse resemblance, and neither was rejected. Finally, a model allowing only for sibling correlations (model 11) was fit; and while it was not rejected, the AIC (8.93) indicated that model 9 provided the most parsimonious fit to the data. For SBP training response at 60 % $\dot{V}O_2$max, and for DBP training responses at both the work rates, no evidence of familial component was found. Similarly, no evidence of familial component for exercise HR and BP training response phenotypes was found in Blacks (data not shown in Table **2**).

Familial correlation estimates (± SE) were computed under the most parsimonious model for each phenotype, which allowed for a single sibling, parent-offspring and spouse correlation. In

Table **2** Model-fitting for submaximal exercise HR and BP training responses in Whites

Model	*Par*	*50 W* *P*	*AIC*	*60 %* *P*	*AIC*
HR Training Response					
1. General hypothesis (fm, fs, fd, ms, md, ss, dd, sd)	8	–––	16.00	–––	16.00
2. No correlations (fm = fs = fd = ms = md = ss = dd = sd = 0)	0	< 0.001	29.42	0.005	22.08
3. No sex differences in offspring (fm, fs = fd, ms = md, ss = dd = sd)	4	0.296	12.92	0.373	12.25
4. No sex differences in parents, offspring (fm, fs = fd = ms = md, ss = dd = sd)	3	0.249	12.64	0.514	10.25
5. No sex and generation differences (fm, fs = fd = ms = md = ss = dd = sd)	2	0.291	11.34	0.635	8.31
6. No sibling correlations (fm, fs, fd, ms, md, ss = dd = sd = 0)	5	0.010	21.35	0.037	18.51
7. No parent-offspring (P-O) correlations (fm, ss, dd, sd, fs = fd = ms = md = 0)	4	0.011	20.97	0.066	16.80
8. No spouse resemblance (fs, fd, ms, md, ss, dd, sd, fm = 0)	7	0.049	17.88	0.020	19.40
9. Single correlation (fm = fs = fd = ms = md = ss = dd = sd)	1	0.362	9.68	0.621	7.32
SBP Training Response					
1. General	8	–––	16.00	–––	16.00
2. No correlations	0	0.043	15.95	0.642	6.04
3. No sex differences in offspring	4	0.253	13.35		
4. No sex differences in parents, offspring	3	0.255	12.57		
5. No sex and generation differences	2	0.341	10.79		
6. No sibling correlations	5	0.045	18.04		
7. No parent-offspring correlations	4	0.156	14.65		
8. No spouse resemblance	7	0.221	15.50		
9. Single correlation	1	0.436	8.93		
10. #9 + no spouse resemblance (fs = fd = ms = md = ss = dd = sd, fm = 0)	1	0.280	10.64		
11. #9 + no P-O and spouse correlations (ss = dd = sd, fm = fs = fd = ms = md = 0)	1	0.119	13.47		
DBP Training Response					
1. General	8	–––	16.00	–––	16.00
2. No correlations	0	0.099	13.41	0.474	7.59

Whites, the correlation was 0.18 ± 0.05 for HR training response at 50 W, 0.15 ± 0.04 for HR training response at 60% $\dot{V}O_2$max, and 0.11 ± 0.04 for SBP training response at 50 W. The corresponding maximal heritability estimates ($h^2 \pm 2SE$) were 34% ± 10% and 29% ± 8% for HR training responses at 50 W and 60% $\dot{V}O_2$max, respectively, and were 22% ± 8% for SBP training response at 50 W.

Discussion

It has been firmly documented that resting HR and BP are influenced by genetic factors [7 – 13]. Genetic contributions to variation in baseline levels of acute HR and BP responses to submaximal exercise are substantial, with heritability of 50% [15]. Wilmore and colleagues have recently reported appreciable reductions of HR and BP levels during submaximal exercise in response to 20 weeks of endurance training in HERITAGE [6]. The observed reductions were greater during submaximal exercise than at rest. The purpose of the present analysis was to assess familial factors that influence these changes in exercise HR and BP in response to training. During submaximal exercise, we found maximal heritabilities of about 20 – 30% for training responses in exercise HR and SBP, and negligible heritability for training responses in exercise DBP. These estimates are independent of the effects of age, sex, BMI, cigarette smoking, $\dot{V}O_2$max and the baseline levels, and are substantially lower than the estimated heritabilities of about 50% for baseline exercise HR and BP in the same data [15]. We also note that the estimates for training responses in exercise HR were slightly higher during submaximal exercise (h^2 = 34% and 29%, at 50 W and 60% $\dot{V}O_2$max, respectively) than at resting (26%), whereas heritability was 22% for training response in exercise SBP in contrast to no significant heritability for training response in resting SBP [14].

In the current study, baseline submaximal exercise HR and BP accounted for up to 40% of the variance in the training response phenotypes. It is therefore not surprising that the familial effect

became modest once the baseline effect was removed in the data adjustment procedure. It is possible that similar genetic component may influence both the baseline and the training response phenotypes. In-depth investigations of this interesting question would be of physiological and clinical importance.

In the present study, we also examined training responses in exercise HR and BP in a total of 257 participants from 113 Black family units (24 fathers, 50 mothers, 64 sons and 119 daughters) in HERITAGE (Table **1b**). However, no significant familial component was found for any of these phenotypes. The smaller sample size of Blacks yields a statistical power of only 48% to detect heritability of about 20% in contrast to a statistical power of 92% for the relatively larger sample size of Whites in HERITAGE. Therefore, the modest but significant heritabilities detected in Whites cannot be ruled out in Blacks. The same phenotypes were also examined at a higher exertion intensity of 80% $\dot{V}O_2$max, and we found no significant familiality in either race (data not shown). It appears that the familial heritabilities displayed a progressive decline from 20 – 30% to undetectable levels as exercise intensity increased from 50 W to 60% $\dot{V}O_2$max to 80% $\dot{V}O_2$max. A similar trend was also noted for pre-training exercise HR and BP phenotypes, going from heritabilities of about 50% at 50 W to about 30% at 60% $\dot{V}O_2$max in these data [15].

It is noteworthy that spouse resemblance is significant and as high as sibling and parent-offspring correlations in this study. Whereas sibling and parent-offspring correlations may suggest the presence of polygenic and common environmental factors, spouse resemblance for these phenotypes may arise on account of shared environment as well as cohabitation effects or assortative mating.

In conclusion, training responses in HR and SBP during submaximal exercise were found to be moderately heritable in Whites. To our knowledge, this constitutes a new finding. However, we failed to find significant familial influences for training responses in exercise HR and BP in Blacks.

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