Heritability of HR and BP response to exercise training in the HERITAGE Family Study

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ABSTRACT

RICE, T., P. AN, J. GAGNON, A. S. LEON, J. S. SKINNER, J. H. WILMORE, C. BOUCHARD, and D. C. RAO. Heritability of HR and BP response to exercise training in the HERITAGE Family Study. *Med. Sci. Sports Exerc.*, Vol. 34, No. 6, pp. 972–979, 2002. **Purpose:** The heritability of the response to exercise training in resting blood pressure (BP) and heart rate (HR) was assessed in 482 Caucasian individuals comprising 98 families participating in the HERITAGE Family Study. **Methods:** All individuals were sedentary at the baseline visit (time 1 measurement). After completing a 20-wk exercise-training program, subjects were measured again (time 2). A familial correlation model was used to assess the heritability (genetic plus familial environmental) of the response in resting systolic BP (SBP), diastolic BP (DBP), and HR, computed as the difference between the two measurement times. This response was adjusted for the effects of baseline levels and age within sex and generation groups. Analyses were conducted separately in a subsample of families in which at least one family member was considered to have elevated BP (95th percentile; SBP $\geq$ 135 or DBP $\geq$ 80). **Results:** Several novel findings emerged from this study. First, the SBP and HR response may be influenced by genetic factors. The maximal heritabilities were 20% (SBP) and 36% (HR) in the elevated BP, 18% and 24% in the complete, and not significant in the normotensive samples. For DBP, there were cohort effects (significant sibling and spouse but not parent-offspring correlations) in the complete and normotensive samples that may be due to generation-specific environmental influences. **Conclusion:** The trainability of SBP and HR in families with elevated BP appears to be determined in part by genetic factors, whereas DBP trainability may be more a function of environmental effects. **Key Words:** SEDENTARY, TRAINABILITY, INTERVENTION, HYPERTENSION

Regular exercise is recognized as an effective non-pharmacological method for reducing essential hypertension (for reviews see 7–13, 17). For example, longitudinal intervention studies show a blood pressure (BP) response to exercise training, with a reduction of about 3/3 mm Hg (systolic BP/diastolic BP) in normotensives, 3/7 mm Hg in borderline hypertensives, and 10/8 mm Hg in hypertensives (see 8 for review). In contrast, heart rate (HR) response to exercise training tends to be related to the measurement conditions. As reviewed by Wilmore et al. (19), little response is observed under ideal resting conditions where the subject is asleep or fully rested. However, a clear response is noted when the resting measures are taken immediately before an exercise test or other stress conditions, suggesting that at least part of the reduction in "resting" HR is in adjusting to the testing environment.

Whether the responses in BP and HR to exercise training aggregate in families is only now being addressed. An intervention study on related individuals is needed in order to evaluate the genetic hypothesis, and only one such study has been reported to date, the HERITAGE Family Study (4). In the HERITAGE Family Study, systolic (SBP) and diastolic BP (DBP) and HR were repeatedly measured both before and after completing a 20-wk (3 times per week) exercise-training protocol with an end target intensity of 75% of the baseline $\dot{V}O_{2max}$ during the last 6 wk. The families were selected to be sedentary at the initial (baseline) visit, with SBP/DBP less than 159/99 mm Hg and no antihypertensive drug therapy.

The major aim of the current study was to investigate whether the responses in HR and BP to training are determined by familial factors. Response was indexed as the difference between time 2 (after training) and time 1 (baseline) values, and was adjusted (within sex and generation groups) for age and baseline levels. In addition, each variable was analyzed in the complete sample, as well as by subsamples stratified by the 95th percentile in BP.

METHODS

Goals. The overall objective of the HERITAGE Family Study is to investigate the role of familial factors underlying

0195-9131/02/3406-0972/$3.00/0
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Submitted for publication June 2001.
Accepted for publication October 2001.

the cardiovascular, metabolic, and hormonal responses to standardized aerobic exercise training. Informed written consent was obtained from each subject, and approval was obtained from the institutional review board of each participating clinical center.

Recruitment. Families were recruited via extensive media publicity and advertisements from four clinical centers. Several criteria were used to screen subjects for participation (see 4 for details). For inclusion in the study, parents were required to be 65 yr of age or younger and offspring between the ages of 17 and 40 yr. All subjects were required to be sedentary at the baseline visit. Sedentary was defined as no regular physical activity over the previous 6 months, including activities lasting 30 min or more involving an energy expenditure of 7 ($\geq$50 yr) or 8 ($<$50 yr) METs, and occurring more than once a week. With a few exceptions approved by a physician, subjects had a body mass index (BMI) $<$ 40 kg·m^{-2} and resting BP did not exceed 159/99 mm Hg (SBP/DBP). There were seven individuals with BMI $\geq$ 40 (values ranging from 40.06 to 47.54 kg·m^{-2}), but no individuals exceeded the BP criteria. Exclusionary criteria on the basis of health centered on ethical concerns regarding maximal exercise testing in previously sedentary subjects. For example, definite or possible coronary heart disease, chronic or recurrent respiratory problems, uncontrolled endocrine or metabolic disorders, or hypercholesterolemia, diabetes, or other conditions or diseases that are life threatening or that could interfere with or be aggravated by cycle exercise were causes for exclusion. The use of antihypertensive medication or lipid-lowering medication (among others) was also cause for exclusion.

Sample characteristics. A total of 529 individuals in 99 families of Caucasian descent were recruited and enrolled in the study. Family structures included the father, mother, and at least three offspring. During the course of the study, 45 individuals dropped out and 2 additional individuals were missing at least one of the BP or HR measures, yielding a final sample size of 482 individuals (233 male and 249 female subjects). Families of African-American descent were also recruited and tested, but are not reported here. The families were stratified according to normotensive and elevated BP status, with elevated BP families defined as having at least one member in the 95th percentile (baseline or posttraining SBP $\geq$ 135 and/or DBP $\geq$ 80) of the HERITAGE cohort. About half of the families met this criterion (family sizes ranged from 2 to 8 individuals, with 85% having 2 parents and at least 2 children), with the remaining families classified normotensive (family sizes ranged from 3 to 6 individuals, with 76% having 2 parents and at least 2 children). Figure 1 depicts the elevated BP (top panel) and normotensive (bottom panel) families. Raw baseline BP is on the y-axis and family ID on the x-axis. Family ID was derived after ranking by SBP family mean, and individuals within families are noted as dots within vertical bars. The horizontal reference lines denote the cutoff criteria (135 for SBP and 80 for DBP). Although selection was based on individual values, the predominant stratification is by family mean, with a few exceptions. For example, a few elevated BP families have lower means, but one or more individuals have extreme values. Likewise, a few normotensive families have somewhat higher means, but the variability within the family is low and no individuals have extreme values.

Exercise-training program. Each subject was trained on a cycle ergometer 3 times per week for 20 wk. Duration and intensity of exercise training was automatically adjusted every 2 wk, as follows. Duration progressively increased from 30 min at baseline to 50 min for the last 6 wk of training, and intensity progressively increased from the HR associated with 55% $\dot{V}O_{2max}$ during baseline to that associated with 75% of baseline $\dot{V}O_{2max}$ for the last 8 wk. The power output of the cycle ergometer was automatically adjusted to the HR response during exercise via a built-in computerized control device. Each training session was supervised on the site and adherence to the protocol was strictly monitored. See Bouchard et al. (4) for further details regarding the study protocol.

Measures. A battery of measurements was administered to each individual both before (time 1) and after (time 2) engaging in the 20-wk standardized exercise-training program. Multiple resting BP and HR measurements were made on 2 separate days at each of time 1 and time 2 visits. Measurements were obtained before 11:00 a.m. with subjects in a 4-h fasted state and with no caffeine or tobacco for at least 2-h before assessment. Measurements were performed in a quiet room after subjects were rested for at least 5-min in a reclining chair with legs elevated and the chair's back reclined at about 45°. BP was determined using a properly fitted cuff connected to a Colin STBP-780 automated unit, and HR also was monitored during this measurement by ECG. At least 4 BP and HR readings were taken after the initial 5-min rest period, with 2-min intervals between readings. The first measurement, although recorded on the paper form, was discarded. The procedure was conducted on 2 separate days for time 1 and on 2 separate days for time 2. Therefore, each of the BP and HR variables represent the average of six measurements (3 measures on each of 2 d) (19,20).

Variable construction and data adjustments. The response variables were computed (time 2 $-$ time 1), and regression analysis was used to remove the effects of age, sex, generation, and baseline levels from this response. The data-adjustment models were developed on the normotensive sample by using stepwise multiple regression. In summary, a response was regressed on the baseline resting value and a cubic polynomial in age, separately in four sex by generation groups (fathers, mothers, sons, and daughters). Only significant terms (5%) were retained. The resulting squared residuals from this mean regression were similarly adjusted for age and initial values in the variance (i.e., heteroscedasticity). The adjusted variable was the residual from the mean regression, divided by the square root of the predicted score from the second regression. A final standardization step ensured zero mean and unit variance. The parameters derived from these models using the normotensive sample were used to construct scores for all individuals, including the elevated BP sample.

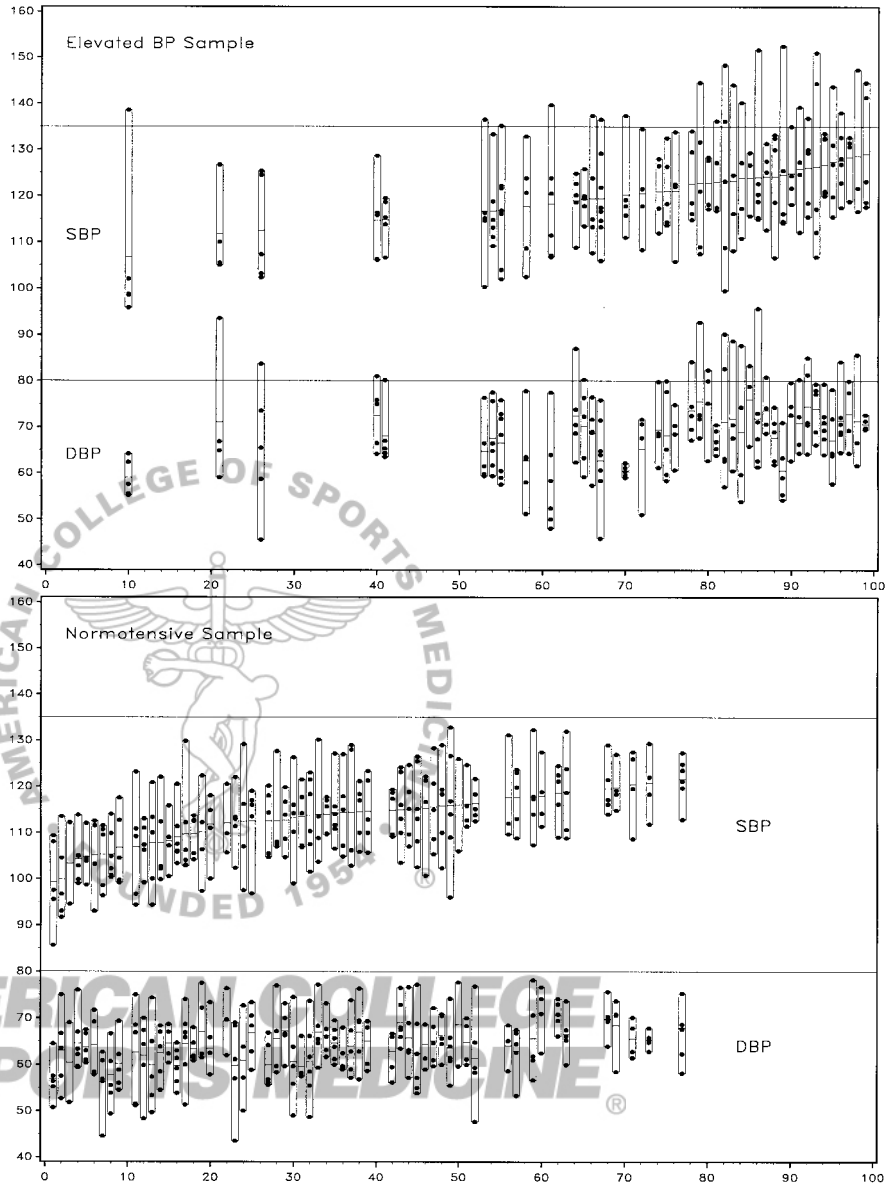

FIGURE 1—Unadjusted SBP and DBP baseline values in the elevated BP (top panel) and normotensive (bottom panel) samples. BP values are on the y-axis with family ID on the x-axis. Each individual is denoted as a *dot* within a family drawn as a *vertical box*. Family ID was determined after ranking by family SBP mean (*horizontal line* within families). The *horizontal reference lines* denote the selection criteria (135 for SBP and 80 for DBP) for stratifying families.

Regarding construction of the analysis variable and the adjustment procedure, it is noted that the baseline and response variables are not independent. The relationship between the two depends not only on the intervention effects (e.g., training) but also on the statistical properties of the repeated assessments (standard deviations at time 1 and time 2) and the correlation between the response and baseline values (see 14). Thus, by adjusting the response for the baseline levels via regression analysis, the effects of initial levels as well as other statistical dependencies between them are removed.

Analysis. The familial aggregation was investigated using a sex-specific familial correlation model developed with the computer program SEGPATH (15). This program fits the model directly to the family data using maximum likelihood methods under the assumption that the phenotypes within a family jointly follow a multivariate normal distribution. The general model was based on four types of individuals [fathers (F), mothers (M), sons (S), and daughters (D)], leading to eight correlations within three familial classes [1 spouse (FM), 4 parent-offspring (FS, FD, MS, MD), and 3 siblings (SS, DD, SD)]. The general model (i.e., all 8 correlations estimated) was fit to the data, as were several reduced models examining sex differences and the significance of the correlations. Null hypotheses were tested using the likelihood ratio test (LRT), which is the difference in minus twice the log-likelihoods (-2 ln L) obtained under the general model and a null hypothesis. The LRT is distributed approximately as a χ^2, with the degrees of freedom equal to the difference in the number of parameters estimated in the two nested models. In addition, Akaike's information criterion (AIC), which is the scaled log likelihood (in this case the χ^2, as all alternative models were compared to the general model) plus twice the number of estimated parameters, was used to compare nonnested models. The "best" model is the one with the smallest AIC (1).

TABLE 1. Means and standard deviations (SDs) for resting measurements by subsample.*

		Elevated BP Families						Normotensive Families					
		Fathers			Mothers			Fathers			Mothers		
Variables	Time	*N*	Means	SD	*N*	Means	SD	*N*	Means	SD	*N*	Means	SD
Parents													
Age (yr)	Time 1	42	55.08	5.48	39	53.63	5.40	50	52.08	4.63[a]	51	50.87	4.52[a]
BMI (kg·m^{-2})	Time 1		28.89	4.82		28.47	5.51		27.87	4.27		26.92	4.05[a]
$\dot{V}O_{2max}$ (mL·min^{-1})	Time 1		2568	418		1601	265[b]		2671	471		1680	258[ab]
	Time 2		2918	472		1894	266[b]		3069	479[a]		1984	296[ab]
	Response		360	217		279	184[b]		397	196		304	160[b]
SBP (mm Hg)	Time 1		129.30	12.34		122.30	12.08[b]		114.68	9.00[a]		112.43	10.13[a]
	Time 2		128.87	12.58		123.50	13.73		115.52	9.34[a]		113.41	9.83[a]
	Response		−0.42	7.92		1.20	8.11		0.83	6.11		0.97	6.73
DBP (mm Hg)	Time 1		76.66	8.72		70.52	6.25[b]		68.75	6.27[a]		65.02	6.08[ab]
	Time 2		76.32	9.20		70.95	7.71[b]		67.99	6.37[a]		64.90	6.41[ab]
	Response		−0.34	5.30		0.43	5.78		−0.77	4.36		−0.12	4.47
HR (beats·min^{-1})	Time 1		64.34	7.68		66.78	8.03		63.00	7.39		66.60	9.37[b]
	Time 2		61.27	7.95		65.27	9.57[b]		58.91	5.64		63.33	8.39[b]
	Response		−3.07	5.27		−1.51	5.75		−4.09	6.06		−3.27	6.49
Offspring		Sons			Daughters			Sons			Daughters		
Age (yr)	Time 1	65	26.79	7.02[c]	70	27.81	6.45[c]	76	24.44	5.31[ac]	89	23.73	5.68[ac]
BMI (kg·m^{-2})	Time 1		26.53	5.90[c]		23.65	4.26[bc]		25.04	3.80[ac]		23.49	4.56[bc]
$\dot{V}O_{2max}$ (mL·min^{-1})	Time 1		3210	429[c]		2061	313[bc]		3372	546[ac]		2066	300[bc]
	Time 2		3709	471[c]		2419	421[bc]		3868	558[ac]		2445	327[bc]
	Response		481	248[c]		357	230[bc]		496	242[c]		380	156[bc]
SBP (mm Hg)	Time 1		121.37	8.60[c]		112.38	7.46[bc]		117.05	8.23[ac]		108.83	7.81[abc]
	Time 2		120.13	8.33[c]		113.77	7.59[bc]		116.83	7.97[a]		108.06	7.55[abc]
	Response		−1.24	5.43		1.40	5.40[b]		−0.22	5.65[a]		−0.77	5.78[ac]
DBP (mm Hg)	Time 1		67.31	8.84[c]		62.82	6.18[bc]		63.81	6.33[ac]		60.93	6.26[abc]
	Time 2		67.93	8.33[c]		63.70	6.04[bc]		63.78	6.61[ac]		60.94	5.38[abc]
	Response		0.63	5.12		0.88	6.01		−0.03	6.08		0.01	5.32
HR (beats·min^{-1})	Time 1		62.50	8.44		65.10	6.98[b]		60.30	8.37[ac]		69.06	9.61[abc]
	Time 2		59.97	8.62		64.47	8.10[b]		55.93	6.99[ac]		65.59	8.79[bc]
	Response		−2.53	5.77		−0.63	7.23[b]		−4.30	6.85[a]		−3.47	6.56[a]

* Time 1 measured in sedentary state (baseline); time 2 measured after 20 weeks of exercise training (post) and response computed as (post − baseline). Elevated BP, at least 1 family member in 95th percentile for BP (SBP ≥ 135 or DBP ≥ 80).
[a] Subsample (elevated BP vs normotensive) differences.
[b] Sex (within generation) group differences.
[c] Generation (within sex) group differences.

Three null hypotheses tested for sex and generation differences: no sex differences in offspring (model 1: FS = FD, MS = MD, SS = DD = SD, df = 4); no sex differences in offspring or parents (model 2: FS = FD = MS = MD, SS = DD = SD, df = 5); and no sex or generation differences (model 3: FS = FD = MS = MD = SS = DD = SD, df = 6). An environmental model positing only a single correlation (model 4: FM = FS = FD = MS = MD = SS = DD = SD, df = 7) was also evaluated. The significance of the familial correlations was tested by familial class: no sibling correlations (model 5: SS = DD = SD = 0, df = 3); no parent-offspring correlations (model 6: FS = FD = MS = MD = 0, df = 4); no spouse correlation (model 7: FM = 0, df = 1); and no familial resemblance at all (model 8: FM = FS = FD = MS = MD = SS = DD = SD = 0, df = 8). Nonrejected hypotheses were combined to form the most parsimonious models, from which the maximal heritability was computed. Maximal heritability (max h^2) was estimated as $[(r_{sibling} + r_{parent\text{-}offspring})(1 + r_{spouse})/(1 + r_{spouse} + (2)(r_{spouse})(r_{parent\text{-}offspring}))]$ (16), and indexes the percentage of variance in the trait due to familial factors. It is considered maximal because it is includes both genetic and familial environmental (if significant) sources of variance, although it is adjusted for degree of spouse resemblance.

We can infer the genetic and environmental sources of this familial variation by examining the pattern of significant spouse, parent-offspring, and sibling correlations. The underlying assumption is that parent-offspring and sibling pairs share 1/2 of their genes in common, whereas spouses share few or no common genes if there is random mating. Therefore, significant parent-offspring and sibling (but not spouse) correlations suggest that the heritable variation may be due primarily to genes. Additional spouse correlations imply that at least part of the resemblance could be due to familial environmental factors (e.g., shared diets and activities).

RESULTS

Training effectiveness. Bouchard et al. (5) described the training effectiveness. For example, there was a significant increase in the mean $\dot{V}O_{2max}$ after training in each of the four sex by generation groups, ranging from 293 mL·min in mothers to 486 mL·min in sons. At the individual level, there were non- and low-responders up to high-responders, with some individuals increasing their $\dot{V}O_{2max}$ by as much as 700 mL·min and up to > 1.0 L·min^{-1}.

Sample statistics and age adjustments. The BP measures were highly reproducible, with technical errors of less than 5.1 mm Hg, coefficient of variations of less than 7%, and intraclass correlations greater than 0.75. The HR measure was only slightly less reproducible (18). Table 1

TABLE 2. Percent variance accounted for by baseline and age in the mean and variance (heteroscedasticity) regressions for the changes in resting SBP, DBP, and HR values.

		Mean Regression		Variance (Heteroscedasticity) Regression	
Variable	Group	Terms	% Variance	Terms	% Variance
SBP	Fathers	Baseline	8.0	None	—
	Mothers	Baseline	14.2	None	—
	Sons	Baseline	14.7	None	—
	Daughters	Baseline	17.2	None	—
DBP	Fathers	Baseline	10.5	Baseline	10.4
	Mothers	Baseline	11.2	None	—
	Sons	Baseline, Age, Age^3	23.5	None	—
	Daughters	Baseline	27.8	None	—
HR	Fathers	Baseline	12.1	None	—
	Mothers	Baseline	11.6	None	—
	Sons	Baseline, Age^2	35.7	Age^3	4.3
	Daughters	Baseline	11.6	None	—

Age^2 is age squared; Age^3 is age cubed.

gives the sample sizes, means and SDs for each of SBP, DBP and HR, separately in four sex by generation groups and separately by elevated BP and normotensive families. Mean group differences were judged by a comparison of SEs. As compared with the normotensive families, the elevated BP families were older and had higher baseline BP levels (as expected) in all four sex by generation groups. The response BP is similar in elevated BP and normotensive families, and for DBP in offspring, but response SBP levels are different across offspring subsamples. Similarly, there are no sample group differences in the response HR for parents, but there is a difference in offspring.

There are no sex differences in the means by using the SE comparison (Table 1) for responses in the parents, although baseline SBP and DBP in the elevated BP families and baseline DBP and HR in the normotensive families are different between mothers and fathers. In these groups, BP is higher in fathers than mothers, and HR is higher in mothers than fathers. For the offspring response variables, male subjects have a greater reduction than female subjects for SBP and HR in the elevated BP sample. There are sex differences for all baseline measures in both offspring samples that are consistent with those in parents (higher BP in male subjects, higher HR in female subjects). Regarding generation differences, the parents tend to have higher baseline levels than the offspring. There are few generation differences in the responses (only for SBP in female subjects in the normotensive sample, with a greater reduction in daughters than in mothers).

The unadjusted baseline and delta (i.e., post training − baseline) variables are negatively correlated in the complete sample (−0.28 for SBP, −0.34 for DBP, and −0.38 for HR) verifying that they are not independent measures. Thus, it is not surprising that baseline levels account for a significant percentage of the variance (between 8% and 35.7% of the variance depending on sex and generation groups) in the response as shown in Table 2.

Familial aggregation. The model-fitting results for SBP are given in the top portion of Table 3. In the complete sample, the only hypotheses that were rejected ($P < 0.05$) were for no sibling correlations (model 5, $P = 0.033$) and no familial correlations at all (model 8, $P = 0.045$). The combined test of the nonrejected hypotheses of no sex differences (model 1), no parent-offspring correlations (model 6), and no spouse correlation (model 7) did not fit by likelihood ratio test ($P = 0.039$). Therefore, the hypothesis with the smallest nonsignificant *P*-value (no sex differences, $P = 0.059$) was removed from the constraints. The revised model (combining models 6 and 7) fit the data by likelihood ratio ($P = 0.212$), but the AIC (13.12) was larger than that for model 4 (all 8 correlations equal, AIC = 12.97). Accordingly, the hypothesis with the next smallest nonsignificant *P*-value (no parent-offspring resemblance, $P = 0.130$) was removed from the constraints. This revised model (combining models 3 and 7) fit by likelihood ratio ($P = 0.177$), was the "best" model by AIC (12.22), and was chosen as most parsimonious. In other words, the best model corresponds to equal parent-offspring and sibling correlations but no spouse resemblance. Because parent-offspring and sibling pairs share both genes and familial environments whereas spouses generally share only the environmental component, this pattern is consistent with the familial effect being primarily a function of genetic factors.

For SBP in the normotensive sample, none of the alternative hypotheses were rejected (i.e., all *P*-values > 0.05). The most parsimonious model by likelihood ratio ($P = 0.856$) and AIC (4.02) was for no familial correlations at all (model 8). For the elevated BP sample, tests for sex and generation differences (models 1 through 3) were borderline, as were the tests for no sibling ($P = 0.110$) and no parent-offspring ($P = 0.076$) correlations, although there was clearly no support for spouse resemblance ($P = 0.749$). Although the hypothesis of no familial resemblance was not rejected by likelihood ratio test (model 8, $P = 0.077$), the AIC for that model (14.19) was larger than that when all eight correlations were equated (model 4, AIC = 13.48). Because the spouse correlations were clearly not significant, an alternative model with $r_{FM} = 0$ and equating the remaining 7 sibling and parent-offspring correlations (models 3 + 7) fit the data by likelihood ratio test ($P = 0.127$), was the "best" model by AIC (13.28), and consequently was chosen as most parsimonious.

The middle portion of Table 3 gives the hypothesis tests for DBP across the different subsamples. The general pattern of results for the complete and normotensive samples was one of significant spouse resemblance and marginal sibship resemblance with no sex differences in the latter (combined models 1 and 6). For the elevated BP sample, none of the correlations were significantly different from zero, and the best model was for no familial resemblance (model 8). The results for HR (bottom portion of Table 3) were quite similar to those for SBP. For the complete and elevated BP samples, there was no spouse resemblance, and the remaining parent-offspring and sibling correlations were equated (models 3 + 7). However, for the normotensive sample, there was no familial resemblance at all (model 8).

TABLE 3. Hypothesis tests for resting BP and HR responses across subsamples.

Trait		Complete		Normotensive		Elevated BP	
Hypotheses	df	*P*	AIC	*P*	AIC	*P*	AIC
SBP response							
1) No sex difference in offspring: FS=FD, MS=MD, SS=DD=SD	4	0.059	17.08	0.798	9.66	0.045	17.32
2) in offspring or parents: FS=FD=MS=MD, SS=DD=SD	5	0.083	15.75	0.882	7.75	0.067	16.32
3) No sex/generation differences: FS=FD=MS=MD=SS=DD=SD	6	0.116	14.21	0.940	5.76	0.081	15.26
4) All 8 correlations equal: FM=FS=FD=MS=MD=SS=DD=SD	7	0.140	12.97	0.845	5.40	0.119	13.48
5) No sibling resemblance: SS=DD=SD=0	3	0.033	18.77	0.695	11.45	0.110	16.03
6) No parent-offspring resemblance: FS=FD=MS=MD=0	4	0.130	15.12	0.859	9.32	0.076	16.48
7) No spouse resemblance: FM=0	1	0.964	14.00	0.324	14.97	0.749	14.10
8) No familial resemblance: FM=FS=FD=MS=MD=SS=DD=SD=0	8	0.045	15.86	0.856	4.02	0.077	14.19
Parsimonious: (1 + 6 + 7) FM=FS=FD=MS=MD=0, SS=DD=SD	7	0.039	16.74				
Parsimonious: (6 + 7) FM=FS=FD=MS=MD=0	5	0.212	13.12				
Parsimonious: (3 + 7) FM=0, FS=FD=MD=MD=SS=DD=SD	7	0.177	12.22			0.127	13.28
Parsimonious: (8) No familial resemblance	8			0.856	4.02		
DBP response							
1) No sex difference in offspring: FS=FD, MS=MD, SS=DD=SD	4	0.530	11.17	0.603	10.73	0.403	12.02
2) in offspring or parents: FS=FD=MS=MD, SS=DD=SD	5	0.336	11.71	0.694	9.04	0.223	12.96
3) No sex/generation differences: FS=FD=MS=MD=SS=DD=SD	6	0.240	11.97	0.196	12.63	0.323	10.98
4) All 8 correlations equal: FM=FS=FD=MS=MD=SS=DD=SD	7	0.101	13.99	0.034	17.15	0.417	9.12
5) No sibling resemblance: SS=DD=SD=0	3	0.075	16.89	0.099	16.28	0.279	13.85
6) No parent-offspring resemblance: FS=FD=MS=MD=0	4	0.608	10.71	0.772	9.81	0.414	11.94
7) No spouse resemblance: FM=0	1	0.013	20.21	0.008	21.14	0.445	14.58
8) No familial resemblance: FM=FS=FD=MS=MD=SS=DD=SD=0	8	0.033	16.76	0.039	16.22	0.389	8.47
Parsimonious: (5 + 6) FS=FD=MS=MD=SS=DD=SD=0	7	0.160	12.55	0.250	11.04		
Parsimonious: (1 + 6) FS=FD=MS=MD=0, SS=DD=SD	6	0.445	8.81	0.672	8.04		
Parsimonious: (8) No familial resemblance	8					0.389	8.47
HR response							
1) No sex difference in offspring: FS=FD, MS=MD, SS=DD=SD	4	0.351	12.43	0.815	9.57	0.118	15.36
2) in offspring or parents: FS=FD=MS=MD, SS=DD=SD	5	0.232	12.85	0.863	7.90	0.075	16.00
3) No sex/generation differences: FS=FD=MS=MD=SS=DD=SD	6	0.335	10.85	0.909	6.11	0.107	14.46
4) All 8 correlations equal: FM=FS=FD=MS=MD=SS=DD=SD	7	0.403	9.25	0.945	4.94	0.088	14.39
5) No sibling resemblance: SS=DD=SD=0	3	0.097	16.31	0.852	10.79	0.016	20.29
6) No parent-offspring resemblance: FS=FD=MS=MD=0	4	0.021	19.56	0.768	9.83	0.012	20.90
7) No spouse resemblance: FM=0	1	0.731	14.12	0.502	14.45	0.514	14.43
8) No familial resemblance: FM=FS=FD=MS=MD=SS=DD=SD=0	8	0.026	17.38	0.910	3.31	0.009	20.50
Parsimonious: (2 + 5 + 7) FM=SS=DD=SD=0, FS=FD=MS=MD	7	0.177	13.53				
Parsimonious: (3 + 7) FS=FD=MS=MD=SS=DD=SD, FM=0	7	0.427	9.02			0.157	12.61
Parsimonious: (8) No familial resemblance	8			0.910	3.31		

The familial correlations under both the general and most parsimonious models are given in Table 4. The maximal heritability (max h^2) ranged from zero (SBP and HR in the normotensive sample and DBP in the elevated BP sample) to 36% for HR in the elevated BP group. The patterns were quite similar for SBP and HR, with significant sibling and parent-offspring but no spouse correlations. The magnitude of the effect is somewhat stronger in the elevated BP

TABLE 4. Familial correlations (±SE) for response under general and parsimonious models.

		SBP			DBP			HR		
		General	Parsim	Max h^2	General	Parsim	Max h^2	General	Parsim	Max h^2
Complete	FM	−0.00 ± 0.11	[0]		0.26 ± 0.10	0.26 ± 0.10		0.04 ± 0.12	[0]	
	FS	−0.18 ± 0.08	0.09 + 0.04		−0.08 ± 0.10	[0]		−0.01 ± 0.10	0.12 ± 0.04	
	FD	0.14 ± 0.09	[0.09]		−0.01 ± 0.09	[0]		0.10 ± 0.09	[0.12]	
	MS	0.16 ± 0.08	[0.09]		0.11 ± 0.10	[0]		0.29 ± 0.09	[0.12]	
	MD	0.12 ± 0.10	[0.09]		0.07 ± 0.09	[0]		0.10 ± 0.09	[0.12]	
	SS	−0.14 ± 0.08	[0.09]		0.29 ± 0.12	0.14 ± 0.07		0.21 ± 0.10	[0.12]	
	DD	0.24 ± 0.10	[0.09]		0.03 ± 0.10	[0.14]		0.04 ± 0.10	[0.12]	
	SD	0.01 ± 0.07	[0.09]	18% ± 0.08	0.08 ± 0.10	[0.14]	14% ± 0.18	0.11 ± 0.09	[0.12]	24% ± 0.08
Normotensive	FM	−0.16 ± 0.15	[0]		0.37 ± 0.12	0.37 ± 0.12		0.10 ± 0.15	[0]	
	FS	0.05 ± 0.12	[0]		−0.17 ± 0.12	[0]		−0.06 ± 0.12	[0]	
	FD	−0.01 ± 0.12	[0]		0.01 ± 0.14	[0]		0.08 ± 0.12	[0]	
	MS	0.10 ± 0.11	[0]		0.05 ± 0.12	[0]		0.12 ± 0.12	[0]	
	MD	0.01 ± 0.13	[0]		0.00 ± 0.14	[0]		0.06 ± 0.12	[0]	
	SS	−0.07 ± 0.15	[0]		0.30 ± 0.14	0.19 ± 0.09		0.11 ± 0.15	[0]	
	DD	0.13 ± 0.15	[0]		0.21 ± 0.17	[0.19]		0.03 ± 0.12	[0]	
	SD	0.06 ± 0.09	[0]	0%	0.00 ± 0.16	[0.19]	19% ± 0.22	−0.06 ± 0.14	[0]	0%
Elevated BP	FM	0.05 ± 0.16	[0]		0.12 ± 0.16	[0]		−0.12 ± 0.18	[0]	
	FS	−0.11 ± 0.11	0.10 + 0.06		−0.05 ± 0.16	[0]		0.06 ± 0.14	0.18 ± 0.06	
	FD	0.28 ± 0.13	[0.10]		−0.06 ± 0.10	[0]		0.00 ± 0.13	[0.18]	
	MS	0.18 ± 0.11	[0.10]		0.26 ± 0.13	[0]		0.51 ± 0.10	[0.18]	
	MD	0.12 ± 0.15	[0.10]		0.11 ± 0.12	[0]		0.13 ± 0.12	[0.18]	
	SS	−0.18 ± 0.08	[0.10]		0.23 ± 0.21	[0]		0.37 ± 0.14	[0.18]	
	DD	0.21 ± 0.13	[0.10]		−0.19 ± 0.12	[0]		−0.02 ± 0.19	[0.18]	
	SD	−0.12 ± 0.12	[0.10]	20% ± 0.12	0.15 ± 0.11	[0]	0%	0.25 ± 0.12	[0.18]	36% ± 0.12

Correlations in square brackets were fixed to zero or equated to a preceding correlation; see text for Max h^2 (maximum heritability).

(20–36%, respectively) than complete sample (18–24%, respectively). For DBP, the results support a familial effect in the complete and normotensive (14–19%) but not elevated BP groups. This familial resemblance is confined to spouse and sibling (but not parent-offspring) pairs, with greater resemblance in the older generation.

DISCUSSION

Our primary purpose in this study was to determine whether the changes in resting BP and HR after 20 wk of endurance exercise training (i.e., trainability or response) were influenced by heritable factors. In addition, we investigated whether the magnitude of these familial effects differed in normotensive families versus those in which one or more members exhibited elevated BP at the initial visit (i.e., in a sedentary state). This question was motivated by previous research suggesting a greater training-induced BP reduction in hypertensive as compared with normotensive subjects (8). We note that while no subjects exhibited moderate or severe (grades 2 or 3) hypertension (i.e., SBP/DBP $>$ 160/100) given our selection criteria, a few depicted in Figure 1 would be classified as high normal ($>$130/85) to mildly hypertensive ($>$140/90), according to the 1999 World Health Organization guidelines (6).

In general, we found evidence of familial aggregation for trainability in SBP and HR. Moreover, familial factors accounted for more variance in the elevated BP sample (20–36%) than in the normotensive (0%) or complete (18–24%) samples. However, SE comparisons suggest that the SBP difference in heritability between the elevated BP and complete samples was not significant. An additional consideration is that of power. In the complete sample there is about 80% power for detecting heritabilities of 17% or more. When the sample is halved (as in the normotensive vs elevated samples), then the heritability must be near 30% to be reliably detected at the same power level. Thus, we cannot rule out significant heritability in the normotensive sample if it is less than 30%, which seems likely given the pattern of results in this study. It is interesting to note that the source of the familial effects for SBP and HR may be primarily genetic since the spouse correlation was negligible. This supports a recent study of SBP and HR responses in these data (3) that reported a putative recessive locus for SBP and major (non-Mendelian) effects for HR in the elevated BP sample. In comparison, another study of this sample (2) yielded maximal heritabilities of 54% and 32% for baseline SBP and HR, respectively. Significant spouse correlations for the baseline measures suggest that at least part of that variance was due to familial environmental factors. Because the response variables analyzed here were constructed so that they were independent of the baseline effect (i.e., removal of the baseline effect via regression analysis), the familial effects for the baseline and response measures may be independent. However, this hypothesis requires further testing in a multivariate format.

The results for resting DBP did not suggest a simple interpretation for the etiological factors underlying the response. There were significant correlations between spouse and sibling (but not parent-offspring) pairs in the complete and normotensive samples. This pattern favors a cohort or age effect that is likely to be environmental in origin. That is, individuals who are more similar in age are more likely to share similar lifestyle habits that may have an impact on the BP response than do individuals who are in different generations or age groups. Although this explanation is the most likely for the spouse correlation, assuming there is random mating for these traits, an alternative explanation in the siblings is that of age-dependent genetic effects. That is, it is possible that different genes are expressed in the offspring than in the parents. The maximal heritability for DBP (probably due in large part to familial environmental factors) ranges from 14 to 19%, with the remaining variance due to unmeasured factors such as specific (nonfamilial) environmental effects. In a previous study of these families (2), the heritability for DBP in the sedentary state was 41%, with a pattern of significant spouse, parent-offspring, and sibling correlations. Together, these results suggest that both genetic and familial environmental factors affect DBP levels in the sedentary state, whereas the response DBP may be due primarily to environmental factors.

Finally, we note that there is little evidence for a mean training response in BP based on the values in Table 1. In fact, a recent report in these HERITAGE families (20) suggests that mean changes in resting BP due to the training are small (generally $<$ 1 mm Hg), being significant in some (e.g., male) but not other (e.g., female) groups. However, although there may be minimal mean response, Figure 2 shows that there is a wide range of response across individuals (from $-$21.7 to $+$26.2). Figure 2 also shows that this variability occurs not only within but between families. The somewhat greater variability between than within families suggests familiality, whereas the pattern of correlations suggests that the response may be due in part to genetic factors.

To put these results into some perspective, we can compute the percentage of variance in the training response due to all known sources of variance in this study. For the SBP response in the elevated sample, 15% (on average) of the total variance is explained by baseline BP level and age. Familial (primarily genetic) factors account for about 20% of the remaining 85%, or alternatively about 17% of the total variance. Thus, over 30% of the total variance can be accounted for by these known factors, leaving $<$ 70% still unexplained. For the HR response, about 20% is due to baseline and age effects, with about 35% of the remaining 80% (or about 30% of the total) due to heritability, leaving about 50% still unaccounted for. Thus, for both SBP and HR, at least half of the explained variance is due to familial factors.

In summary, baseline level, age and familial factors account for between 30–50% of the variance in SBP and HR training responses. Thus, some individuals with elevated BP may be more likely than others to derive cardiovascular benefits from exercise training in part because of their initial levels or age, but also in part because of their genetic propensity. Studies investigating the molecular basis for the

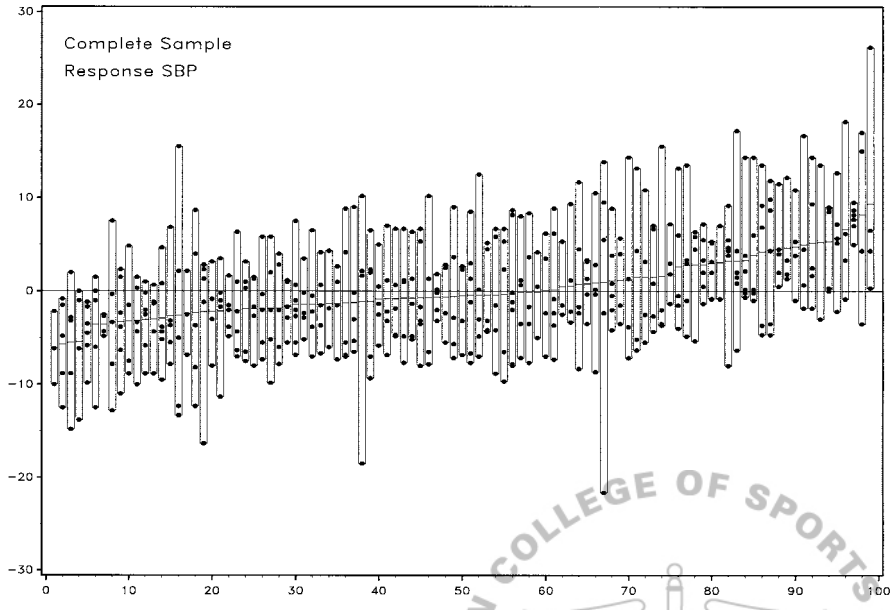

FIGURE 2—Unadjusted SBP response values (post training − baseline value) for the complete sample. See Figure 1 for details. Family ID was determined after ranking by mean family response. The *horizontal reference line* at zero indicates no training response.

genetic component are warranted. Moreover, these results suggest that genetic factors should be considered in investigations searching for additional sources of variance underlying training responses.

The HERITAGE study is supported by the NHLBI through the following grants: HL45670 (C. Bouchard, PI), HL47323 (A. S. Leon, PI), HL47317 (D. C. Rao, PI), HL47327 (J. S. Skinner, PI), and HL47321 (J. H. Wilmore, PI). C. Bouchard is partly funded by the MRC of Canada-Roche Canada Donald B. Brown Research Chair on Obesity. A. Leon is partly funded by the Henry L. Taylor Professorship in Exercise Science and Health Enhancement.

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