Familial Aggregation of Stroke Volume and Cardiac Output During Submaximal Exercise: The HERITAGE Family Study

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Familial aggregation of stroke volume (SV) and cardiac output (Qc by CO_2 rebreathing) at 50 Watts (W) and 60 % of maximal oxygen uptake ($\dot{V}O_2$max) as well as their changes in response to a 20-week endurance exercise training program was assessed in 99 Caucasian families who participated in the HERITAGE Family Study. In order to interpret familial influences independent of effects of age, sex, and body size (indexed by body surface area here), SV and Qc levels were adjusted for these primary parameters prior to genetic analysis within four sex-by-generation groups (the responses to training were additionally adjusted for their baseline values). Maximal heritabilities for baseline SV, Qc, and their changes in response to training during the two stages of submaximal exercise were estimated using a familial correlation model. At 50 W, maximal heritabilities reached 41 % and 42 % for baseline SV and Qc, respectively, and were 29 % and 38 % for the respective responses to training. At 60 % of $\dot{V}O_2$max, maximal heritabilities reached 46 % for baseline SV and Qc, and were 24 % and 30 % for the respective responses to training. Generally there were no meaningful differences between the maximal heritabilities at 50 W and 60 % of $\dot{V}O_2$max. However, the maximal heritabilities for the baseline were slightly higher than the estimates for the changes in response to training. Based upon results arising from these non-obese, non-hypertensive, and sedentary families, we found that SV and Qc at 50 W and 60 % of $\dot{V}O_2$max as well as their changes in response to the 20-week endurance exercise training were moderately heritable. Not only genetic determinants but also familial non-genetic factors might attribute to the observed patterns of familial aggregation of SV and Qc during submaximal exercise in the present study.

Key words: 50 W, 60 % of $\dot{V}O_2$max, endurance training, maximal heritability.

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Introduction

It is presently known that both cardiorespiratory fitness and increased levels of physical activity are independently associated with a reduced risk for cardiovascular disease (CVD) [8,9,12]. Maximal oxygen consumption ($\dot{V}O_2$max) is frequently employed to index levels of cardiorespiratory fitness. The latter is reportedly to be negatively associated with CVD risk factor profile, CVD mortality, and all-cause mortality in men and women [4]. By definition, $\dot{V}O_2$max hemodynamically is the product of cardiac output (Qc) and arterial-mixed venous oxygen difference (a-vO_2 diff), i.e. $\dot{V}O_2$ = QC × a-vO_2 diff. Cardiac output is simply the product of stroke volume (SV) and heart rate (HR) (Qc = SV × HR). Increases in $\dot{V}O_2$ max with exercise training are primarily the result of increases in Qc, which, in turn, results from an increase in SV max [22]. It is therefore important to understand the genetic and familial non-genetic determinants of baseline SV, Qc, and the responses to training during submaximal exercise. It is known that there are familial determinants for resting HR. For example maximal heritabilities ranged from 32 % to 34 % for baseline resting HR [2,13] and was 26 % for its response to training in the HERITAGE Family Study [15]. Further, An et al. found evidence of a major locus effect for baseline resting HR and a major non-Mendelian effect for its response to training in the same study [3]. In contrast to HR no studies have been performed previously to report familial influences on SV and Qc at rest or during exercise.

In the present study we assessed the role of genetic and familial non-genetic factors on SV and Qc measured during submaximal exercise at 50 W and 60 % of $\dot{V}O_2$max before and after completing a 20-week endurance exercise training program. Familial aggregation of HR together with systolic blood pressure (SBP) and rate pressure product (RPP, HR×SBP) measured during submaximal exercise was reported separately in the HERITAGE Family Study [11].

Materials and Methods

Sample

The HERITAGE Family Study was designed to investigate the role of the genotype in cardiovascular, metabolic, and hormonal responses to aerobic exercise training and the contribution of regular exercise to changes in cardiovascular disease and diabetes risk factors. A description of the HERITAGE Family

Study protocol, population, and inclusion and exclusion criteria has been published [5].

A total of 438 individuals from 99 two-generation white families (214 men and 224 women) were available for analyses of baseline SV and Qc whereas a total of 424 individuals (206 men and 218 women) had complete data allowing computation of the response to training. Table **1** gives the sample sizes within four sex-by-generation subgroups (fathers, mothers, sons, and daughters) for baseline SV and Qc and the changes in response to training. Black families were also recruited and tested in the HERITAGE Family Study. Their results will be reported separately to assess racial difference in the pattern of familial aggregation.

Exercise training program

Following the initial test battery, subjects completed a 20-week endurance training program (3 days per week for a total of 60 exercise sessions) on cycle ergometers (SensorMedics ErgoMetrics 800S, Yorba Linda, CA) which were computer-controlled to maintain the participants' heart rates at levels associated with fixed percentages of their $\dot{V}O_2$max. The training program started at 55% of $\dot{V}O_2$max for 30 minutes per session and gradually increased to 75% of $\dot{V}O_2$max for 50 minutes per session during the last 6 weeks of training. The full test battery was administered again at the conclusion of the training program. All training sessions were supervised on site, and adherence to the protocol was strictly monitored.

Submaximal exercise test and measurements

Submaximal exercise tests at 50 W and at 60% of $\dot{V}O_2$max (two stages) were conducted on a cycle ergometer. Subjects exercised 8–12 minutes at an absolute (50 W) and at a relative power output equivalent to 60% of $\dot{V}O_2$max. As to the latter there is a linear relationship between $\dot{V}O_2$ and power output. Once we had the data on $\dot{V}O_2$ at each power output and the $\dot{V}O_2$max, we plotted the values for each subject and determined which power output was associated with 60% of that subject's $\dot{V}O_2$max. During submaximal exercise two HR and Qc measurements on separate days both before and after the 20-week endurance training program were obtained and averaged across the two tests at 50 W and 60% of $\dot{V}O_2$max. HR was

Table 1 Means and SD for age, BSA, SV, Qc at 50 W and at 60% of $\dot{V}O_2$max

Variables	No.	Means	SD	No.	Means	SD
		Fathers			Mothers	
Age (years)	85	53.5#	5.5	82	52.0#	5.0
BSA (m^2)	85	2.1*	0.2	82	1.8*,#	0.2
		Sons			Daughters	
Age (years)	129	25.4#	6.1	142	25.7#	6.5
BSA (m^2)	129	2.0*	0.2	142	1.7*,#	0.2
50 W		Fathers			Mothers	
Baseline						
SV (ml/beat)	85	103.9*,#	16.6	82	84.6*	12.7
Qc (l/min)	85	10.9#	1.6	82	10.6	1.4
Response to training						
SV (ml/beat)	83	2.8	10.3	78	4.1	9.1
Qc (l/min)	83	– 0.6	1.2	78	– 0.7	0.9
		Sons			Daughters	
Baseline						
SV (ml/beat)	129	111.0*, #	17.3	142	86.7*	14.9
Qc (l/min)	129	11.7*, #	1.5	142	10.9	1.3
Response to training						
SV (ml/beat)	123	3.0	14.0	140	3.4	9.7
Qc (l/min)	123	– 0.6	1.2	140	– 0.6	1.0
60% of $\dot{V}O_2$max		Fathers			Mothers	
Baseline						
SV (ml/beat)	85	108.1*,#	18.1	82	84.5*	12.7
Qc (l/min)	85	13.8*, #	2.2	82	10.8*, #	1.6
Response to training						
SV (ml/beat)	83	10.6#	11.2	78	7.9	9.2
Qc (l/min)	83	0.8	1.4	78	0.5#	1.2
		Sons			Daughters	
Baseline						
SV (ml/beat)	129	118.9*, #	20.0	142	86.4*	15.8
Qc (l/min)	129	17.3*, #	2.7	142	12.9*, #	2.0
Response to training						
SV (ml/beat)	123	14.4*, #	12.8	140	10.3*	11.1
Qc (l/min)	123	1.2	1.7	140	1.2#	1.5

#: Significant ($P < 0.05$) mean differences for father-son or mother-daughter (within sex) comparisons.
*: Significant ($P < 0.05$) mean differences for father-mother or son-daughter (within generation) comparisons

calculated from an electrocardiogram, and values were recorded once steady state had been achieved at 50 W and 60% of $\dot{V}O_2$max. Steady state was defined as a plateau or a point where there was little variation in HR. This generally occurred during the first 3–4 minutes at a new power output. Qc was determined using the Collier [7] CO_2 re-breathing technique as described by Wilmore et al. [20]. SV was derived from Qc and HR (SV = Qc/HR). A detailed description of the exercise test methodology has been reported recently by Skinner et al. [18] .

Data adjustments

In the present study baseline SV and Qc at 50 W and 60% of $\dot{V}O_2$max were significantly correlated with age (r = – 0.15 to – 0.40, P < 0.002), sex (r = – 0.20 to – 0.59, P = 0.0001), and body surface area (BSA, r = 0.35 to 0.53, P = 0.0001). BSA (m^2, weight $(kg)^{0.5378}$ × height $(cm)^{0.3164}$ × 0.024265) [10,16] is considered to be the best estimate of body size whereas body mass index (BMI, weight [kg]/height $[m]^2$) is more related to fatness. To assess familial influences independent of potential effects rendered by these primary co-variates, baseline SV and Qc were adjusted for the effects of a polynomial in age (linear, quadratic, and cubic) and BSA within each of the four sex-by-generation groups on both the mean and the variance (e.g. heteroscedasticity) using a stepwise multiple regression procedure. Likewise SV and Qc responses to training were adjusted for the effects of a polynomial in age (age, age^2, and age^3), BSA, and the baseline values. For each of the regressions only terms that were significant at the 5% level were retained. Each of the adjusted phenotypes was finally standardized to a mean of zero and a SD of one.

Familial resemblance

A preliminary test for familial aggregation was undertaken with an analysis of variance (ANOVA). The ANOVA was performed on the adjusted phenotypes (e.g. baseline SV and Qc, or the responses to training) as the dependent variable and family ID as the independent variable.

The computer program SEGPATH [14] was used to fit the sex-specific familial correlation model directly to the family data using the method of maximum likelihood. The general model was based on 4 subgroups (fathers [f], mothers [m], sons [s], and daughters [d]) giving rise to 8 correlations in 3 familial classes (1 spouse [fm], 4 parent-offspring [fs, fd, ms, md], and 3 sibling [ss, dd, sd]). Each null hypothesis was tested by a comparison to the general model using the likelihood ratio test (LRT), which is the difference in minus twice the log-likelihood (– 2 In L) obtained under the two models. In addition to the LRT, Akaike's Information Criterion (AIC), which is – 2 In L plus twice the number of estimated parameters, was used to compare non-nested models [11]. The 'best' model is the one with the smallest AIC.

Sex and generation differences in correlations were tested in model 2 (no sex differences in offspring, fs = fd, ms = md, ss = dd = sd), model 3 (no sex differences in parents or offspring, fs = fd = ms = md, ss = dd = sd), and model 4 (no sex and no generation differences, fs = fd = ms = md = ss = dd = sd) (see Table **4**). The significance of various components of the familial resemblance was examined in model 5 (no sibling correlations, ss = dd = sd = 0), model 6 (no parent-offspring correlations, fs = fd = ms = md = 0), and model 7 (no spouse resemblance, fm = 0). Finally a single correlation was fit to the data by equating all 8 correlations in model 8. A parsimonious model was determined by combining the non-rejected hypotheses into a single test (e.g. model 9, fm = 0, fs = fd, ms = md, ss = dd = sd = 0; model 10, fm = fs = fd = ms = md, ss = dd = sd = 0; model 11, fm = 0, fs = fd = ms = md = ss = dd = sd). Maximal heritability was computed using the familial correlations from the most parsimonious model. This estimate includes both polygenic and familial environmental sources of variance and is adjusted for the degree of spouse resemblance.

Results

In this study coefficients of variation for repeated measurements were 7.6% and 7.2% for SV and Qc at 50 W, respectively, and were 6.9% and 5.9% for SV and Qc at 60% of $\dot{V}O_2$max, respectively. Intraclass correlations were 0.87 and 0.76 for SV and Qc at 50 W, respectively, and were 0.91 and 0.93 for SV and Qc at 60% of $\dot{V}O_2$max, respectively [21]. Thus the phenotypes were measured with high reproducibility and good precision, which is necessary for a meaningful interpretation of the responses to training.

Means and SD of the unadjusted baseline SV and Qc and the changes in response to training are presented in Table **1**. Significant age, BSA, and baseline terms with percentages of variance accounted for in each of the four sex-by-generation groups are presented in Table **2**. In general, BSA was a significant predictor of baseline SV, Qc, and the responses to training except that it was not a significant predictor of Qc response to training at 60% of $\dot{V}O_2$max. Baseline variables were significant predictors of the changes in response to training. Age was solely a significant predictor of Qc at 60% of $\dot{V}O_2$max (in fathers and offspring for the baseline and in daughters for the response to training).

The ANOVA results are presented in Table **3**. Baseline, the F-ratios ranged from 2.16 to 2.34 (P < 0.01) with 38% – 40% of the variance accounted for by family membership. Relative to the responses to training, the F-ratios ranged from 1.55 to 2.17 (P < 0.01) with 32% – 40% of the variance accounted for by family membership. These results suggest that baseline SV, Qc, and their responses to training aggregate in families.

The model-fitting results are presented in Table **4**. For baseline SV and Qc at 50 W, models 2 – 4 were not rejected suggesting no sex and generation differences in the correlations. Models 5 – 7 were rejected (P < 0.05) which suggested the presence of significant sibling, parent-offspring as well as spouse resemblance (with no sex and generation differences). The hypothesis of a single correlation (model 8) was not rejected and provided the most parsimonious fit to the data according to the LRT and AIC. For baseline SV at 60% of $\dot{V}O_2$max, each of the constrained hypotheses (models 2 – 6 and model 8) was rejected except for the hypothesis of no spouse resemblance (model 7), and the latter provided the most parsimonious fit to the data according to the LRT. For baseline Qc at 60% of $\dot{V}O_2$max, there were no sex and no generation differences (models 2 – 4 were not rejected). Sibling and parent-offspring correlations were significant (models 5 – 6 were rejected) while spouse resemblance was not significant (model 7 was not rejected). Although the hypothesis of a single correlation (model

Table 2 Data adjustments for baseline SV, Qc, and the responses to training

Effects	Group	Significant terms	% Var.	Significant terms	% Var.
Baseline		50 W		60 % of $\dot{V}O_2$max	
SV	fathers	BSA	15.50	BSA	16.60
	mothers	BSA	7.78	none	none
	sons	none	none	BSA	3.12
	daughters	BSA	26.04	BSA	25.67
Qc	fathers	BSA	15.13	age, BSA	21.60
	mothers	BSA	11.88	none	none
	sons	none	none	age^3, BSA	7.61
	daughters	BSA	20.15	BSA, age	20.70
Response		50 W		60 % of $\dot{V}O_2$max	
SV	fathers	BSA, base	17.63	base	5.21
	mothers	base	13.64	none	none
	sons	base	17.91	BSA, base	21.07
	daughters	base	14.95	base	9.66
Qc	fathers	BSA, base	42.79	base	6.86
	mothers	BSA. base	37.93	base	8.70
	sons	base	26.49	base	21.60
	daughters	base	25.39	age, age^2, base	13.20

Table 3 The comparisons of the between-family and within-family components

Variable	R^2	F-value	P
50 W			
Baseline:			
SV*	0.40	2.26	0.0001
Qc	0.40	2.34	0.0001
The responses to training:			
SV	0.35	1.75	0.0001
Qc	0.40	2.17	0.0001
60 % of $\dot{V}O_2$max			
Baseline:			
SV	0.38	2.16	0.0001
Qc	0.40	2.33	0.0001
The responses to training:			
SV	0.32	1.55	0.0026
Qc	0.34	1.68	0.0004

*: The F value indicates that there is a 2.26 times more variance (P = 0.0001) between than within families in the age-adjusted SV at 50 W with 40 % of the variance being accounted for by family membership

8) was rejected, it was further tested in the absence of spouse resemblance (model 11), and the latter provided the 'best' fit to the data according to the LRT and AIC.

According to the LRT and AIC the most parsimonious hypothesis was model 2 (no sex difference in offspring) for SV response to training at 50 W. Whereas hypotheses 2 – 8 were all rejected, the general model actually provided the most parsimonious fit for the data for Qc response to training at 50 W. At 60 % of $\dot{V}O_2$max a single correlation model fit each of SV and Qc responses to training while a single correlation hypothesis with no spouse resemblance (model 11) was the most parsimonious.

Parameter estimates (correlations ± SE) are given in Table **5** under both the general and the most parsimonious hypotheses for each of the phenotypes. The maximal heritabilities, which include both genetic and non-genetic familial sources of variance (see footnote in Table **5**), ranged from 41 % – 46 % for the baseline measures and 24 % – 38 % for the responses to training.

Discussion

In the present study SV increased about 3 – 4 ml/beat at the absolute rate of work (50 W) and about 8 – 14 ml/beat at the relative rate of work (60 % of $\dot{V}O_2$max) in response to training during submaximal exercise. While baseline Qc levels during submaximal exercise considerably increased, Qc changes in response to training were very modest (close to zero), ranging from – 0.6 to – 0.7 l/min at 50 W to 0.5 to 0.8 l/min at 60 % of $\dot{V}O_2$max. Detailed results for age, sex, and race differences of SV and Qc changes consequent to the 20-week endurance training during submaximal exercise were reported by Wilmore et al. in a separate study in the HERITAGE Family Study [23]. The results in the current study are physiologically consistent with our common understanding that Qc is maintained by decreasing HR but increasing SV levels consequent to regular exercise [6,17,20]. In this study the mean Qc changes in response to training were modest but they may cluster in families, i.e. we cannot conclude that there is no familial effect just because the overall mean change in response to training is near zero.

To the best of our knowledge heritability estimates based on family studies, twin studies, and other particular cohort studies for SV and Qc during submaximal exercise have never been reported in the research literature. The present study therefore represents the first attempt to assess familial effects on SV and Qc during submaximal exercise. As stated above, maximal her-

Table 4 Model-fitting summary for SV and Qc at 50 W and 60 % of $\dot{V}O_2$max

Model	df	Baseline χ^2	P	AIC	Responses χ^2	P	AIC
SV av 50 W							
1. General	0	–	–	16.00	–	–	16.00
2. No sex differences in offspring	4	8.87	0.064	16.87	5.45	0.244	13.45
3. No sex dif. in parents, offspring	5	10.11	0.072	16.11	13.89	0.016	19.89
4. No sex, generation differences	6	10.16	0.118	14.16	14.11	0.028	18.11
5. No sibling correlations	3	17.90	< 0.001	27.90	6.31	0.097	16.31
6. No parent-offspring correlations	4	18.47	< 0.001	26.47	18.20	0.001	26.20
7. No spouse resemblance	1	6.22	0.013	20.22	2.44	0.118	16.44
8. Single correlation	7	10.52	0.161	12.52	14.12	0.049	16.12
9. model 5 + model 7 + model 8	6				11.96	0.063	15.96
Qc at 50 W							
1. General	0	–	–	16.00	–	–	16.00
2. No sex differences in offspring	4	4.94	0.294	12.94	11.15	0.025	19.15
3. No sex dif. in parents, offspring	5	4.95	0.422	10.95	13.20	0.022	19.20
4. No sex, generation differences	6	5.71	0.456	9.71	13.21	0.040	17.21
5. No sibling correlations	3	11.31	0.010	21.31	13.67	0.003	23.67
6. No parent-offspring correlations	4	25.71	< 0.001	33.71	15.81	0.003	23.81
7. No spouse resemblance	1	3.95	0.047	17.95	6.95	0.008	20.95
8. Single correlation	7	5.76	0.568	7.76	14.38	0.045	16.38
SV at 60% of $\dot{V}O_2$max							
1. General	0	–	–	16.00	–	–	16.00
2. No sex differences in offspring	4	9.85	0.043	17.85	5.04	0.283	13.04
3. No sex, dif. in parents, offspring	5	16.19	0.006	22.19	7.38	0.194	13.38
4. No sex, generation differences	6	18.67	0.005	22.67	7.39	0.286	11.39
5. No sibling correlations	3	25.72	< 0.001	35.72	5.01	0.171	15.01
6. No parent-offspring correlations	4	18.16	0.001	26.16	10.34	0.035	18.34
7. No spouse resemblance	1	2.24	0.134	16.24	0.08	0.777	14.08
8. Single correlation	7	18.68	0.009	20.68	7.93	0.339	9.93
9. model 5 + model 7 + model 8	7				10.45	0.164	12.45
10. model 5 + model 8	7				9.80	0.200	11.80
11. model 7 + model 8	7				7.44	0.385	9.44
QC at 60% of $\dot{V}O_2$max							
1. General	0	–	–	16.00	–	–	16.00
2. No sex differences in offspring	4	7.59	0.108	15.59	5.06	0.281	13.06
3. No sex dif. in parents, offspring	5	10.48	0.063	16.48	5.07	0.407	11.07
4. No sex, generation differences	6	11.32	0.079	15.32	5.11	0.530	9.11
5. No sibling correlations	3	22.15	< 0.001	32.15	8.17	0.043	18.17
6. No parent-offspring correlations	4	21.54	< 0.001	29.54	9.74	0.045	17.74
7. No spouse resemblance	1	0.22	0.639	14.22	0.03	0.862	14.03
8. Single correlation	7	14.35	0.045	16.35	6.21	0.515	8.21
11. model 7 + model 8	7	11.65	0.113	13.65	5.15	0.642	7.15

itabilities reflect collective effects of not only genetic determinants but also non-genetic familial factors. After adjusting for the degree of spouse resemblance and the effects of age, sex, and body size, they reached 41 % – 46 % for SV and Qc during submaximal exercise. They were slightly lower (24 % – 38 %) for their responses to training independent of the effects of age, sex, body size, and their baseline values. These results provided evidence of significant familial aggregation and suggested that both SV and Qc during submaximal exercise are moderately heritable in these primarily non-obese and non-hypertensive Caucasian families. Our heritabilities are basically the maximized estimates. Compared to a general sample

Table 5 Parameter estimates and SE under general and most parsimonious models

Parameters	Baseline		Responses to training	
	General	Most parsimonious	General	Most parsimonious
SV at 50 W				
fm	0.27 ± 0.10	0.22 ± 0.05	0.18 ± 0.11	0.17 ± 0.11
fs	0.30 ± 0.09	(0.22)	– 0.06 ± 0.10	0.04 ± 0.07
fd	0.25 ± 0.09	(0.22)	0.13 ± 0.09	(0.04)
ms	0.13 ± 0.11	(0.22)	0.33 ± 0.09	0.29 ± 0.06
md	0.24 ± 0.09	(0.22)	0.23 ± 0.08	(0.29)
ss	0.40 ± 0.11	(0.22)	0.28 ± 0.02	0.13 ± 0.07
dd	0.30 ± 0.12	(0.22)	– 0.02 ± 0.13	(0.13)
sd	0.04 ± 0.11	(0.22)	0.11 ± 0.09	(0.13)
h^2		41 %*		29 %#
Qc at 50 W				
fm	0.22 ± 0.11	0.23 ± 0.05	0.32 ± 0.11	0.32 ± 0.11
fs	0.38 ± 0.08	(0.23)	0.11 ± 0.11	0.11 ± 0.11
fd	0.17 ± 0.09	(0.23)	0.19 ± 0.10	0.19 ± 0.10
ms	0.22 ± 0.09	(0.23)	0.37 ± 0.09	0.37 ± 0.09
md	0.29 ± 0.09	(0.23)	0.14 ± 0.12	0.14 ± 0.12
ss	0.27 ± 0.12	(0.23)	0.45 ± 0.12	0.45 ± 0.12
dd	0.21 ± 0.10	(0.23)	0.11 ± 0.11	0.11 ± 0.11
sd	0.13 ± 0.11	(0.23)	0.14 ± 0.11	0.14 ± 0.11
h^2		42 %		38 %
SV at 60 % of $\dot{V}O_2$max				
fm	0.17 ± 0.11	(0)	0.04 ± 0.12	(0)
fs	0.30 ± 0.10	0.31 ± 0.09	– 0.08 ± 0.11	0.12 ± 0.05
fd	0.28 ± 0.08	0.26 ± 0.09	0.14 ± 0.09	(0.12)
ms	– 0.05 ± 0.11	– 0.09 ± 0.11	0.14 ± 0.11	(0.12)
md	0.14 ± 0.09	0.10 ± 0.09	0.24 ± 0.09	(0.12)
ss	0.51 ± 0.10	0.51 ± 0.10	0.30 ± 0.14	(0.12)
dd	0.28 ± 0.10	0.27 ± 0.10	0.04 ± 0.13	(0.12)
sd	0.16 ± 0.11	0.16 ± 0.11	0.10 ± 0.10	(0.12)
h^2		46 %		24 %
Qc at 60 % of $\dot{V}O_2$max				
fm	0.05 ± 0.12	(0)	0.02 ± 0.12	(0)
fs	0.32 ± 0.09	0.23 ± 0.04	0.08 ± 0.11	0.15 ± 0.04
fd	0.31 ± 0.08	(0.23)	0.22 ± 0.08	(0.15)
ms	0.11 ± 0.11	(0.23)	0.09 ± 0.12	(0.15)
md	0.19 ± 0.09	(0.23)	0.16 ± 0.09	(0.15)
ss	0.58 ± 0.10	(0.23)	0.33 ± 0.13	(0.15)
dd	0.22 ± 0.12	(0.23)	0.02 ± 0.12	(0.15)
sd	0.23 ± 0.10	(0.23)	0.14 ± 0.09	(0.15)
h^2		46 %		30 %

*: Maximum heritability computed as: $[(r_{sibling} + r_{parent\text{-}offspring})(1 + r_{spouse})/(1 + r_{spouse} + 2 \times r_{spouse} \times r_{parent\text{-}offspring})]$, includes both genetic and familial environmental sources of variance and is adjusted for the degree of spouse resemblaance. #: Heritabilities for SV response to training at 50 W were 17 % for father-offspring and 39 % for mother-offspring

with both physically active and inactive individuals, the sedentary families used in the present study may have comprised a more homogeneous sample. Exercise is an important and potential environmental factor, it is certainly of interest to compare our estimates with those from other studies which are more representative of general populations, if available in the future, where SV and Qc variations are not minimized by controlling physical inactivity.

Qc is maintained and regulated by changes of HR along with changes of SV. Results from several family studies have also consistently suggested that familial factors similarly influence HR levels. Heritabilities were about 32 % – 33 % [2,13] with a major gene effect [3] for resting HR, and the estimate reached 26 % for its response to training [15]. The estimates for baseline HR during submaximal exercise were reported separately (52 % at 50 W and 45 % at 60 % of $\dot{V}O_2$ max) along with SBP and RPP which strongly relates to myocardial oxygen requirements and coronary blood flow in the HERITAGE Family Study [11].

Parent-offspring and sibling correlations are usually employed to account for genetic effect as well as non-genetic familial effect. In contrast, spouse resemblance is frequently explained by familial environmental effect although assortative mating for body size (relative weight), food preferences, physical inactivity, and other lifestyle factors may also contribute in part to it. In this study it is interesting to note that spouse resemblance was significant for SV and Qc (baseline and the changes in response to training) at 50 W but non-significant at 60 % of $\dot{V}O_2$ max. This would suggest that with subjects exercising at higher power output (60 % of $\dot{V}O_2$ max *versus* 50 W), the spouse resemblance diminished, which may reflect relatively stronger

or additional genetic influences on SV and Qc at 60% of $\dot{V}O_2$ max. In fact the familial resemblance for SV response to training at 60% of $\dot{V}O_2$max is driven primarily by the parent-offspring rather than sibling resemblance (see P-values in Table **4**). Nevertheless the heritability estimates (and SE) for SV and Qc (see Table **5**) were in the same magnitude for the two rates of work during submaximal exercise but in general were slightly higher for baseline measures *versus* their changes in response to training.

The noteworthy finding from the present study is that these hemodynamic phenotypes frequently used in patient assessments and clinical studies have familial determinants during two stages of submaximal exercise. Whereas the source of this familial aggregation may well involve genetic effects, shared environmental impacts cannot be ruled out on the basis of the current study, particularly in light of the significant spouse resemblance for some of these measurements.

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References

[1] Akaike H. A new look at the statistical model identification. IEEE Trans Automat Control 1974; 19: 716 – 723
[2] An P, Rice T, Gagnon J, Borecki IB, Pérusse L, Leon AS, Skinner JS, Wilmore JH, Bouchard C, Rao DC. Familial aggregation of resting blood pressure and heart rate in a sedentary population: The HERITAGE Family Study. Am J Hypertens 1999; 12: 264 – 270
[3] An P, Rice T, Gagnon J, Borecki IB, Leon AS, Skinner JS, Wilmore JH, Bouchard C, Rao DC. Complex segregation analysis of resting blood pressure and heart rate measured before and after a 20-week endurance exercise training program: The HERITAGE Family Study. American Journal of Hypertension 2000; 13: 488 – 497
[4] Blair SN, Kampert JB, Kohl HW 3rd, Barlow CE, Macera CA, Paffenbarger Jr RS, Gibbons LW. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. JAMA 1996; 27: 205 – 210
[5] Bouchard C, Leon AS, Rao DC, Skinner JS, Wilmore JH, Gagnon J. The HERITAGE Family Study: Aims, design and measurement protocol. Med Sci Sports Exerc 1995; 27: 721 – 729
[6] Charlton GA, Crawford MH. Physiologic consequences of training. Cardiology Clinics 1997; 15: 345 – 354
[7] Collier CR. Determination of mixed venous CO_2 tensions by rebreathing. J Appl Physiol 1956; 9: 25 – 29
[8] Farrel SW, Kampert JB, Kohl HW III, Barlow CE, Macera CA, Paffenbarger Jr RS, Gibbsons LW, Blair SN. Influences of cardiorespiratory fitness levels and other predictors on cardiovascular disease mortality in men. Med Sci Sports Exerc 1998; 30: 899 – 905
[9] Haddock BL, Hopp HP, Mason JJ, Blix G, Blair SN. Cardiorespiratory fitness and cardiovascular disease risk factors in postmenopausal women. Med Sci Sports Exerc 1998; 30: 893 – 898
[10] Haycock GB, Schwartz GJ, Wisotsky DH. Geometric method for measuring body surface area: A height-weight formula validated in infants, children, and adults. J Pediatr 1978; 93: 62 – 66
[11] Leon AS, An P, Rice T, Pérusse L, Gagnon J, Wilmore JH, Skinner JS, Rao DC, Bouchard C. Familial determinants of cardiovascular responsiveness to submaximal exercise in the sedentary state: The HERITAGE Family Study. Annals of Behavioral Medicine, submitted
[12] McMurray RG, Ainsworth BE, Harrell JS, Griggs TR, Williams OD. Is physical activity or aerobic power more influential on reducing cardiovascular disease risk factors. Med Sci Sports Exerc 1998; 30: 1521 – 1529
[13] Pérusse L, Leblanc C, Bouchard C. Inter-generation transmission of physical fitness in the Canadian population. Canadian Journal of Sports Sciences 1988; 13: 8 – 14
[14] Province MA, Rao DC. General purpose model and a computer program for combined segregation and path analysis (SEGPATH): Automatically creating computer programs from symbolic language model specifications. Genet Epidemiol 1995; 12: 203 – 219
[15] Rice T, An P, Gagnon J, Leon AS, Skinner JS, Wilmore JH, Bouchard C, Rao DC. Familial aggregation of changes in resting heart rate and blood pressure in response to endurance exercise training: The HERITAGE Family Study. Medicine and Science in Sports and Exercise, submitted
[16] Simone GD, Devereux RB, Daniels SR, Mureddu GF, Roman MJ, Kimball TR, Greco R, Witt S, Contaldo F. Stroke volume and cardiac output in normotensive children and adults: Assessment of relations with body size and impact of overweight. Circulation 1997; 95: 1837 – 1843
[17] Singer M. Cardiac output in 1998. Heart 1998; 79: 425 – 428
[18] Skinner JS, Wilmore KM, Jaskolska A, Jaskolski A, Daw EW, Rice T, Gagnon J, Leon AS, Wilmore JH, Rao DC, Bouchard C. Reproducibility of maximal exercise test data in the HERITAGE Family Study. Med Sci Sports Exerc 1999; 31: 1623 – 1628
[19] Turley KR. Cardiovascular responses to exercises in children. Sports Med 1997; 24: 241 – 257
[20] Wilmore JH, Farrell PA, Norton AC, Coté RW 3rd, Coyle EF, Ewy GA, Tempkin LP, Billing JE. An automated indirect assessment of cardiac output during rest and exercise. J Appl Physiol 1982; 52: 1493 – 1497
[21] Wilmore JH, Stanforth PR, Turley KR, Gagnon J, Daw EW, Leon AS, Rao DC, Skinner JS, Bouchard C. Reproducibility of cardiovascular, respiratory, and metabolic responses to submaximal exercise: The HERITAGE Family Study. Med Sci Sports Exerc 1998; 30: 259 – 265
[22] Wilmore JH, Costill DL. Physiology of sport and exercise. Champaign, IL: Human Kinetics, 1999; 2nd edition: 277 – 297
[23] Wilmore JH, Stanforth PR, Gagnon J, Rice T, Mandel S, Leon AS, Rao DC, Skinner JS, Bouchard C. Changes in cardiovascular function during submaximal exercise consequent to 20 weeks of endurance training by race, sex and age: The HERITAGE Family Study. Journal of Applied Physiology, submitted

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