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Changes in Exercise Capacity of Cardiac Asymptomatic Hereditary Hemochromatosis Subjects over 5-Year Follow up

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Abstract

Objective—A long-term effect of hereditary hemochromatosis (HH) on aerobic exercise capacity (AEC) has not been well described.

Design—Forty-three HH and 21 volunteer control (VC) subjects who were asymptomatic underwent cardiopulmonary exercise testing using the Bruce protocol. AEC was assessed with minute ventilation (V_E), oxygen uptake (VO_2), and carbon dioxide production (VCO_2) at baseline (BL) at a 5-year follow up (5Y) assessment. A paired t-test was used for analyses of normality data; otherwise, a Wilcoxon signed rank sum test was used.

Results—Thirty-three HH subjects and 18 VC subjects returned for a repeat CPX at 5Y (80% overall return rate). At 5Y, AEC was not different between the two groups. As compared with BL measurements, exercise time, peak VO_2 , and the V_E/VCO_2 slope did not differ statistically at 5Y between both groups. Iron depletion by phlebotomy for 5 years did not significantly affect AEC in newly diagnosed HH subjects at baseline ($n=14$) and cardiac arrhythmias during exercise tended to decrease after 5 years of therapy in this group.

Conclusions—The AEC of asymptomatic HH subjects treated with conventional therapy is not statistically affected by the disease over a 5-year period.

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Keywords

Hereditary Hemochromatosis; Exercise Capacity; Cardiopulmonary Exercise Test; Prospective Study

Hereditary hemochromatosis (HH) is the most common metabolic genetic disorder and affects approximately one in 180 members of the Caucasian population.^{1,2} We have previously reported that the aerobic exercise capacity of cardiac asymptomatic HH subjects was similar to that of age-gender matched normal volunteers at one cross sectional time point.³ Iron overload, which is induced by HH, has been shown to cause diastolic and systolic dysfunction⁴ and the long-term effect of HH on aerobic exercise capacity has not been reported, although this would be of interest for healthcare professionals. It is of special interest for those who monitor athletes with HH since a higher frequency of HFE (hemochromatosis gene) mutations which cause HH is reported among endurance runners.⁵

In addition, the long-term effectiveness of conventional phlebotomy therapy in preventing HH associated complications such as hypothyroidism, liver malignancy, arthritis, systolic and diastolic cardiac dysfunction, and cardiac arrhythmias is not well elucidated.⁶⁻⁸ Likewise, the long-term therapeutic benefit of conventional phlebotomy therapy on aerobic exercise capacity has not been reported. We had an opportunity to serially track the aerobic exercise capacity of cardiac asymptomatic subjects with HH, whose baseline observations were reported in this journal, under NHLBI-sponsored "Heart Study of Hemochromatosis (NCT00068159)" over a 5-year span. Thus, we now report on the changes in aerobic exercise capacity at 5-year follow up in the HH subjects who received conventional phlebotomies over this period in comparison with volunteer control subjects.

METHODS

Study Subjects

The study was conducted at the Clinical Center of the National Institutes of Health. Forty-three subjects with HH and 21 age and gender-matched healthy controls were initially recruited to participate in a National Heart, Lung, and Blood Institute (NHLBI) Institutional Review Board approved protocol, 03-H-0282 (NCT00068159), between September 2003 and August 2005. All subjects provided written informed consent and the protocol was consistent with the principles of the Declaration of Helsinki.⁹ Eligibility criteria for study participation among HH subjects included: 1) age 21 years or older, 2) asymptomatic 3) genetic studies showing homozygosity for the C282Y HFE gene mutation, 4) documented evidence of iron overload with serum ferritin levels > 400 mg/L or transferrin saturation > 60%, and 5) absence of significant end-organ damage secondary to HH. Study eligibility for control subjects included: 1) age 21 years or older, 2) NYHA functional class I, 3) genetic studies showing absence of C282Y or H63D mutations in the HFE gene, and 4) normal ferritin and transferrin saturation levels. All subjects with excessive alcohol ingestion, uncontrolled hypertension, diabetes requiring insulin or more than one oral hypoglycemic agent, tobacco use in the past three months, and/or beta-adrenergic blocker or calcium channel blocker use were excluded from our study. Patients were recruited with the assistance of the NIH Clinical Center Patient Recruitment and Public Liaison Office and via direct mailings of study information to physicians (Appendix). All subjects were contacted for 5-year (5Y) follow-up and all HH subjects were treated under current therapeutic phlebotomy guidelines.^{10,11}

Cardiopulmonary Exercise Testing

Treadmill cardiopulmonary exercise testing (CPX) was performed using the Bruce protocol.¹² Electrocardiography (ECG) tracings, clinical symptoms, blood pressure, and respiratory gas analysis were recorded continuously throughout the test. Workload was expressed as metabolic equivalents (METs) by dividing peak oxygen consumption (VO_2), in $\text{mLO}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, by 3.5. Simultaneous respiratory gas analysis was performed using breath by breath analysis of O_2 and CO_2 on a Carefusion Vmax Spectra 229c instrument (Carefusion, San Diego, CA).^{3,13,14} The oxygen and carbon dioxide sensors were calibrated before each exercise test. The ventilatory sensor was likewise calibrated prior to each exercise test using a 3-liter syringe. Minute ventilation (V_E), VO_2 and carbon dioxide production (VCO_2) were measured. The peak VO_2 was defined as the highest 20 second-averaged VO_2 achieved during exercise and the peak respiratory exchange ratio (RER), the ratio between VCO_2 and VO_2 , was also calculated from the same interval. Peak VO_2 was normalized to age and gender using the formula published by Jones et al.¹⁵ Ventilatory threshold (VT) was determined using the V-slope analysis method.¹⁶ The V_E/VCO_2 slope, a parameter used to assess ventilatory efficiency during exercise,^{17–21} was calculated as previously described¹⁹ because HH has been linked to cardiac dysfunction.⁴ A V_E/VCO_2 slope <30 is considered a normal response to exercise.^{17–19, 21}

Exercise ECG Response

An abnormal ischemic exercise electrocardiogram was defined by a cardiologist (YS) using conventional criteria of 1 mm of horizontal or downsloping ST segment depression for at least 80 ms after the end of QRS complex.²³ A complex arrhythmia was defined as ventricular couplets, ventricular tachycardia, or supraventricular tachycardia.

Statistical Analysis

A paired Student t-tests were used to compare measurements between HH and controls; however, the non-parametric Wilcoxon Rank Sum test was applied when normality of data could not be established. To compare baseline measurements with those at 5Y, a paired Student t-test was used. The effect of iron-depletion phlebotomy therapy was ascertained using paired Student t-tests. For categorical data, a χ -square test was used to compare measurements between baseline and 5Y and HH and control subjects at the same time point. Data are expressed mean $\pm$ S.D. A p-value <0.05 was considered to be statistically significant. The data consistency was confirmed with a 2×2 repeated measures ANOVA design evaluating group $\times$ time interaction when a statistical significance was detected.

RESULTS

Baseline Characteristics

No subject was censored between baseline and 5Y follow-up evaluation. Nine HH and 3 control subjects were lost to follow-up and one HH subject declined to have a follow-up CPX test. Among 33 HH subjects who completed the 5Y follow-up, 19 were in the stable maintenance phase of phlebotomy therapy with steady iron levels and 14 were newly diagnosed subjects at baseline.²⁴ Both HH and control groups contained a similar proportion of female subjects (33% vs. 32%, HH subjects vs. control subjects) and the details of the baseline characteristics have been published previously.²⁵ The mean age was comparable between the HH and control group (51 ± 10 vs. 50 ± 8 years) at baseline. The average age of control drop-outs was significantly younger than that of the entire control group (39 ± 3 vs. 48 ± 8 years, $p < 0.01$). Otherwise, the drop-outs were comparable demographically to those in their respective study groups (data not shown). The HH subjects who completed 5Y follow up demonstrated significantly higher transferrin saturation at baseline and 5Y as

compared to controls (Table 1). Ferritin and aspartate aminotransferase decreased from baseline at 5Y in HH subjects.

Exercise Performance Parameters

Aerobic exercise performance, measured by exercise time, peak VO_2 , VT, HR and hemodynamic responses, did not differ significantly between HH and control subjects at 5Y (Table 2). In addition, the V_E/VCO_2 slope was comparable between the groups at 5Y (Table 2). Peak RER, the gold standard index of exercise effort,²¹ was also comparable between the groups and indicated excellent exercise effort. At 5Y, peak RER slightly decreased from baseline in HH subjects from baseline although the mean value was still consistent with maximal effort. On the other hand, peak VO_2 normalized to age and sex and VT slightly increased in HH subjects at 5Y compared with baseline. These changes were not observed in control subjects (Table 2).

Exercise ECG Responses at 5Y

The incidence of an abnormal ischemic ECG response at 5Y was no longer significant in asymptomatic HH subjects as compared with control subjects (39% vs. 33% of subjects) in contrast to the baseline as we previously published.³ Complex cardiac arrhythmias tended to occur more frequently in asymptomatic HH subjects (24% vs. 17% subjects), but it did not reach a statistical significance.

Effect of Phlebotomy on Exercise Performance for Newly Diagnosed HH Subjects

Fourteen newly diagnosed HH subjects at the time of recruitment completed repeat CPX after 5 years of phlebotomy therapy. As seen in the 6 month follow-up of this cohort in our previous report,³ exercise capacity measured with exercise time, peak VO_2 , VT, and the V_E/VCO_2 slope did not change significantly at the extended period of 5Y treatment (Figure 1). In addition, the incidence of cardiac arrhythmias during exercise tended to decrease after 5 years of phlebotomy therapy in this group (50% vs. 21%, data are before and after phlebotomy therapy, $P=0.111$). In addition, these main findings did not change if the 5Y missing values were imputed with mean levels for the group (data not shown) and significant results were confirmed with a significant group $\times$ time interaction by a 2×2 repeated measure ANOVA (data not shown).

DISCUSSION

Our study at 5Y follow-up demonstrates that: 1) overall aerobic exercise capacity and ventilatory efficiency in cardiac asymptomatic HH subjects was not statistically different from that seen in healthy control subjects; 2) iron removal by 5Y of phlebotomy therapy did not affect aerobic exercise capacity as compared with control subjects.

Iron overload due to HH has been reported to cause both systolic and diastolic dysfunction in studies in which the average age was 50 to 53 years and the average duration from diagnosis was 13 months to 4 years.^{26–28} Once systolic dysfunction is documented, aerobic exercise capacity becomes compromised.^{26,27} We have previously demonstrated that cardiac asymptomatic HH subjects have a similar aerobic exercise capacity compared to apparently healthy control subjects.³ However, it was not clear at that point whether this would be a consistent finding at long-term follow-up since we have found that these HH subjects continue to be exposed to elevated levels of oxidative stress even as iron levels are improved,²⁹ and oxidative stress may affect aerobic exercise capacity through modulation of left ventricular diastolic function.³⁰ In addition, long-term follow-up data on aerobic exercise capacity in this population can be helpful in determining the effectiveness of current phlebotomy therapy regimens. Our study shows that overall aerobic exercise

capacity continues to be comparable to normal subjects in asymptomatic HH subjects treated with chronic phlebotomy therapy at 5Y follow-up.

Although we speculated that an elevated iron level is detrimental to aerobic exercise capacity, there is a conflicting view suggesting the possible beneficial effect of increased iron on exercise performance.⁵ We have previously reported that the lack of a significant association between the iron levels and aerobic exercise capacity parameters suggests that iron levels are an unlikely determinant of functional performance.³ Our follow up results further support our previous observation.

The higher incidence of ischemic ECG changes were noted in HH subjects in our baseline evaluation³, our previous report revealed that none of the asymptomatic subjects with ischemic ECG responses demonstrated abnormal left ventricular wall motion assessed with echocardiography during symptom-limited supine bicycle exercise.^{3,24} Furthermore, 50% of abnormal ST responses of HH subjects were transient, lasting less than one minute. Our 5Y follow-up data show that approximately one-third of HH subjects have ST depression with exercise, but the incidence of ischemic ECG responses is no longer significantly higher in HH subjects. At 5Y follow-up, 43 % of abnormal ST responses in HH subjects and 55 % of those in control subjects were transient, lasting less than one minute. This may be in part explained by an increase in false positive ECG changes during exercise in control subjects over 5Y follow-up reaching a similar frequency as those in HH subjects at baseline.

Complex cardiac arrhythmias during exercise are not significantly different between HH and control subjects at 5Y follow-up. This may be in part related to a tendency of decreased cardiac arrhythmias generally in newly diagnosed HH subjects who were treated for 5 years by phlebotomy.

Limitations

Our study size was too small to allow comparisons of aerobic exercise capacity in different clinical subsets, such as male vs. female. Also, it is possible that a larger study may detect slight differences in aerobic exercise capacity between HH and control subjects. Self reported joint pain was more frequent in HH subjects as compared with normal subjects at baseline³, and, although this was not assessed at 5Y, this might have affected exercise performance in HH subjects given that peak RER slightly decreased at 5Y in HH subjects. However, joint discomfort being the reason for exercise termination was infrequently reported by HH subjects and was comparable to control subjects at 5Y follow-up (9% in HH subjects, 6% in control subjects, $P=0.654$). Our subjects' exercise habits were not matched between HH and control groups and this might introduce bias into the results.

The sample number of this study is even smaller than our original publications investigating aerobic exercise capacity in asymptomatic HH subjects due to attrition during the 5Y follow-up, and it is possible that the associated hypotheses of interest were underpowered. It is also possible that the younger age of drop-outs in control subjects could have an effect on the main study conclusions. In addition, a statistical analysis of multiple variables can increase a chance of coincidental statistical significance.

In conclusion, our study shows that aerobic exercise capacity is comparable between cardiac asymptomatic HH subjects and normal controls after 5Y follow-up. Further, investigation is warranted to assess an even longer-term effect of HH on aerobic exercise capacity.

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Figure 1. Effect of induction phlebotomy on exercise performance. Black bars denote baseline (BL) measurements of metabolic exercise parameters and white bars denote the same measurements after iron removal by 5-year of phlebotomy therapy. Error bars are S.D.

Table 1
Clinical Characteristics of Hereditary Hemochromatosis and Control Groups over 5 Years

Variables	HH		Controls		P values	
	BL	5Y	BL	5Y	5Y	5Y
Age (years)	51 ± 10	56 ± 10 [*]	50 ± 8	55 ± 8 [*]		0.704
Gender (female)	11(33%)	11(33%)	6(32%)	6(32%)		>0.999
Heart rate (bpm)	78 ± 11	72 ± 10 [*]	74 ± 11	69 ± 12		0.383
Systolic BP (mmHg)	123 ± 16	127 ± 16	124 ± 14	129 ± 18		0.620
Diastolic BP (mmHg)	77 ± 12	76 ± 11 [†]	82 ± 10	83 ± 11		0.040
Height (cm)	175 ± 9	174 ± 11	173 ± 9	171 ± 11		0.465
Weight (kilogram)	88 ± 15	87 ± 18	80 ± 18	80 ± 15		0.137
BSA (m ²)	2.0 ± 0.2	2.0 ± 0.2	1.9 ± 0.2	2.0 ± 0.3		0.422
Ferritin (μg/L) [#]	536 ± 752	55 ± 60 [*]	88 ± 72	96 ± 73		0.075
Transferrin sat (%)	54 ± 25 [†]	50 ± 22 [†]	23 ± 8	26 ± 11		<0.001
Hemoglobin (g/dL)	14.2 ± 1.4	15.4 ± 5.2	14.4 ± 1.1	14.4 ± 0.9		0.300
Hematocrit (%) [#]	42.9 ± 4.2	44.1 ± 9.0	42.3 ± 3.4	43.3 ± 2.9		0.408
ALT (IU/mL) [#]	39 ± 25	35 ± 15	27 ± 13	34 ± 11		0.962
AST (IU/mL) [#]	31 ± 11	22 ± 11 [*]	25 ± 5	20 ± 7 [*]		0.538
Glucose (mg/dL)	96 ± 14	107 ± 38	101 ± 11	98 ± 11		0.211
Creatinine (mg/dL)	0.9 ± 0.2	0.9 ± 0.3	1.0 ± 0.2	0.9 ± 0.2		0.297
LVEDV (ml)	79 ± 22	82 ± 29	72 ± 14	71 ± 21		0.117
LVESV (ml)	26 ± 10	30 ± 13	26 ± 3	26 ± 10		0.234
LVEF (%)	67 ± 7	65 ± 7	64 ± 5	65 ± 7		0.961

BL=baseline, 5Y=5-year follow up, HH=subjects with hereditary hemochromatosis homozygous for C282Y, HR=heart rate, bpm=beats per minute, BSA=body surface area, sat=saturation, Hgb=hemoglobin, Hct=hematocrit, ALT=alanine aminotransferase, AST=aspartate aminotransferase. P values=p values driven from a paired t-test comparing HH with control subjects at 5Y. See Methods for statistical analyses. n=33 for HH and n=19 for controls at baseline and 5Y. LV=left ventricular, LVEDV=L V end-diastolic volume, LVESV=L V end-systolic volume, LVEF=L V ejection fraction. LVEDV, LVESV, and LVEF were measured with echocardiography.

^{*} P<0.05 vs. BL.

[†] P<0.05 vs. controls. Data are expressed as mean ± SD.

[#] Normality was not observed.

Table 2

Exercise performance parameters at baseline and 5-year follow up.

Variables	HH		Control		P values
	BL	5Y	BL	5Y	
Exercise time (sec) [#]	603 ± 135	607 ± 208	655 ± 147	699 ± 186	0.092
Peak heart rate (bpm)	173 ± 18	166 ± 16	172 ± 13	167 ± 18	0.938
Peak systolic BP (mmHg)	179 ± 24	181 ± 28	166 ± 21	170 ± 29	0.173
Peak diastolic BP (mmHg)	72 ± 16	71 ± 12	75 ± 9	76 ± 12	0.187
Peak RPP (10 ³ ·mmHg·bpm)	30.8 ± 4.9	30.1 ± 5.3	28.5 ± 3.9	28.2 ± 5.0	0.206
Heart rate recovery (bpm)	24.6 ± 7.8	26.9 ± 8.9	24.4 ± 7.5	25.2 ± 9.1	0.548
Workload, METs	8.5 ± 2.0	8.5 ± 2.2	9.2 ± 1.5	9.3 ± 2.0	0.230
Peak VO ₂ (mL·kg ⁻¹ ·min ⁻¹)	29.8 ± 7.1	29.8 ± 7.8	32.2 ± 5.4	32.5 ± 7.0	0.230
Peak VO ₂ -Normalized (%)	95.2 ± 17.2	103.6 ± 20.1 [*]	103.8 ± 21.7	114.1 ± 28.0	0.173
Ventilatory threshold (mL·kg ⁻¹ ·min ⁻¹)	20.0 ± 5.1	23.0 ± 11.5 [*]	21.0 ± 5.1	21.0 ± 4.3	0.387
VE/VCO ₂ slope [#]	23.9 ± 2.1	24.0 ± 2.2	23.3 ± 4.5	23.8 ± 3.2	0.701
VE max (L·min ⁻¹)	98.3 ± 33.7	90.5 ± 29.5	91.5 ± 26.0	93.7 ± 26.6	0.670
Peak RER	1.24 ± 0.10	1.10 ± 0.20 [*]	1.20 ± 0.10	1.17 ± 0.11	0.148

HH: hereditary hemochromatosis (HH) subjects with C282Y homozygous mutation, metabolic equivalent (METs) workload was calculated from dividing the actual measurement of peak VO₂ by the metabolic rate constant 3.5 mL O₂·min⁻¹·kg⁻¹, BP=blood pressure, RPP=rate pressure product, VE=minute ventilation, VCO₂=respiratory CO₂ content, RER=respiratory exchange ratio, P values=p values driven from a paired t-test comparing HH with control subjects at 5Y. Heart rate recovery was measured at 1 min of recovery stage. Data are mean ± SD. The data between groups were compared by a paired Student t-test. n=33 for HH and n=19 for controls at baseline and 5Y.

^{*} p<0.05 vs. BL with a paired t-test.

[#] Normality was not observed.