Heritability, Linkage, and Genetic Associations of Exercise Treadmill Test Responses

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Background—The blood pressure (BP) and heart rate responses to exercise treadmill testing predict incidence of cardiovascular disease, but the genetic determinants of hemodynamic and chronotropic responses to exercise are largely unknown.

Methods and Results—We assessed systolic BP, diastolic BP, and heart rate during the second stage of the Bruce protocol and at the third minute of recovery in 2982 Framingham Offspring participants (mean age 43 years; 53% women). With use of residuals from multivariable models adjusted for clinical correlates of exercise treadmill testing responses, we estimated the heritability (variance-components methods), genetic linkage (multipoint quantitative trait analyses), and association with 235 single-nucleotide polymorphisms in 14 candidate genes selected a priori from neurohormonal pathways for their potential role in exercise treadmill testing responses. Heritability estimates for heart rate during exercise and during recovery were 0.32 and 0.34, respectively. Heritability estimates for BP variables during exercise were 0.25 and 0.26 (systolic and diastolic BP) and during recovery, 0.16 and 0.13 (systolic and diastolic BP), respectively. Suggestive linkage was found for systolic BP during recovery from exercise (locus 1q43–44, log-of-the-odds score 2.59) and diastolic BP during recovery from exercise (locus 4p15.3, log-of-the-odds score 2.37). Among 235 single-nucleotide polymorphisms tested for association with exercise treadmill testing responses, the minimum nominal probability value was 0.003, which was nonsignificant after adjustment for multiple testing.

Conclusions—Hemodynamic and chronotropic responses to exercise are heritable and demonstrate suggestive linkage to select loci. Genetic mapping with newer approaches such as genome-wide association may yield novel insights into the physiological responses to exercise. (Circulation. 2007;115:2917-2924.)

Key Words: blood pressure ■ exercise ■ genetics ■ heart rate

Exercise treadmill testing (ETT) is a well-established method to detect signs of ischemic heart disease in asymptomatic patients.1 More recently, ETT response measures have been shown to predict a range of cardiovascular events such as new-onset hypertension,2,3 cardiovascular morbidity and mortality,4–9 sudden death,10 and all-cause mortality in asymptomatic patients.5,8,11–13 Specifically, chronotropic incompetence,6,12 blood pressure (BP) and heart rate (HR) response during exercise,2,3,5,10 and BP and HR during recovery after exercise3,5,7,10 are some of the variables that have been associated with adverse outcomes. Further, several studies have indicated that ETT characteristics could improve cardiovascular disease risk prediction beyond that of the global Framingham risk score or the European counterpart, Systematic Coronary Risk Evaluation (SCORE).14–16

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Interindividual variability in ETT response measures may be caused by genetic influences, environmental determinants, or a combination of both. In particular, definition of the
genetic determinants of ETT traits may yield novel insights into the physiological response to exercise and the pathological
conditions predicted by ETT. In a report from the HERITAGE family study (HEalth, RIsk factors, exercise Training And GEnetics), several chromosomal regions with potential genetic linkage for hemodynamic exercise characteristics were found. Previous genetic association studies have been limited by a focus on 1 or a limited number of candidate genes, by small selected study samples, or by nonconventional exercise testing protocols. At present, the genetic determinants of ETT measures with a standard Bruce protocol are largely unknown.

Accordingly, using a large community-based sample, we evaluated the heritability and linkage of ETT measures and performed comprehensive association analyses to examine if variation in 14 candidate genes from the neurohormonal pathways influences interindividual variation in ETT measures.

Methods

Study Sample

The design and selection criteria of the Framingham Offspring study have been previously described. The second examination (1978 to 1982) comprised 3863 participants. This examination included an ETT in addition to a physician-obtained medical history, routine physical examination, 12-lead ECG, and biochemical tests (such as glucose and lipid profile).

Subjects were excluded from the present study for the following reasons: prevalent cardiovascular disease (n = 165), chronic obstructive lung disease (n = 93), valvular disease (n = 24), resting ST-segment abnormality (n = 2), use of cardiac glycoside or β-blockers (n = 119), age < 20 years at index examination (n = 10), inadequate or missing ETT data (n = 254), inability to complete the first stage of the Bruce protocol (n = 80), interrupted ETT as a result of an ischemic response (n = 33), hypotension (n = 3), chest pain (n = 4), and arrhythmia during exercise (n = 94). After these exclusions, 2982 participants (1586 women) remained eligible for the present study. The heritability analyses were based on 2053 participants (1058 women) from 949 extended families with at least 2 members. The largest 291 families (1068 individuals, 543 women) were genotyped with a 10-cM–density genome scan by the Mammalian Genotyping Service laboratory at the Marshfield Clinic (Marshfield, Wis; marker set 8A, average heterozygosity 0.77; http://research.marshfieldclinic.org/genetics), as previously described. The association analyses were based on 1227 unrelated participants (randomly selected to include only 1 participant from each family), who provided blood samples for DNA extraction during the sixth clinical examination (1995 to 1998). Redundant SNPs were genotyped to help assess for linkage disequilibrium block structure similarity between reference panel and Framingham Heart Study sample and in the event of genotype failures. Linkage disequilibrium plots for each of the 14 genes are available at http://cardiogenomics.med.harvard.edu/genes/gene-list. Any SNPs genotyped that were not in Hardy–Weinberg equilibrium (P < 0.01) were not included in the analyses.

Exercise Testing Protocol

The participants underwent a submaximal ETT according to the standard Bruce protocol while their ECGs were continually monitored and recorded (simultaneous V1 and V5; Clinical Data Inc, Newton, Mass) during exercise and for 4 minutes into the recovery period after exercise. Exercise was terminated when the participants reached their target HR (85% of their age- and sex-predicted maximal HR), and the participants immediately got off the treadmill and rested in a supine position. Exercise testing was terminated prematurely for the following reasons: limiting chest discomfort, dyspnea, fatigue, or leg discomfort; hypotension or a severe hypertensive response; or the development of significant ECG abnormalities such as an ischemic ST-segment response.

The Bruce protocol ETT phenotypes examined in the study were defined as follows:

1. Systolic BP during the second stage of exercise (measured once at the middle of the stage)
2. Diastolic BP during the second stage of exercise (measured once at the middle of the stage)
3. HR during the second stage of exercise (measured once at the middle of the stage)
4. Systolic BP at the third minute of the recovery phase
5. Diastolic BP at the third minute of the recovery phase
6. HR at the third minute of the recovery phase

With the definition of the exercise phenotypes at the second stage of the Bruce protocol, we standardized the duration of exercise before assessment of BP and HR. Also, most participants reached this level of exercise, which leads to enhanced generalizability. BP and HR were assessed at the third minute of the recovery phase to maintain consistency with previous studies.

Tag Single-Nucleotide Polymorphism Selection and Genotyping Methods

The 14 genes in the association analyses were selected from the CardioGenomics project (http://cardiogenomics.med.harvard.edu/pga-overview), the objective of which was to examine genetic factors associated with echocardiographic left heart structure and function. Genes from the neurohormonal pathways were selected a priori for their potential involvement in hemodynamic and chronotropic responses to exercise and included the following genes: ADRA1A, ADRA1B, ADRA1D, ADRB1, ADRB2, ACE, AGTR1, AGTR2, AGT, NPPA, NPPB, NPR1, NPR2, REN (Table I in the online-only Data Supplement). The rationale for gene selection from these pathways was that the neurohormonal systems are known to be important in the regulation of BP and HR, and that most of the prior genetic association studies of hemodynamic response to exercise have focused on single genes in these pathways with conflicting results.

In a reference DNA panel, we characterized the linkage disequilibrium structure for common single-nucleotide polymorphisms (SNPs) at each locus and selected tag SNPs as previously described. The Sequenom MassARRAY platform (Sequenom, Inc, San Diego, Calif) was used to genotype the tag SNPs in the Framingham Heart Study sample, which consisted of 1227 unrelated participants (randomly selected to include only 1 participant from each family), who provided blood samples for DNA extraction during the sixth clinical examination (1995 to 1998). Redundant SNPs were genotyped to help assess for linkage disequilibrium block structure similarity between reference panel and Framingham Heart Study sample and in the event of genotype failures. Linkage disequilibrium plots for each of the 14 genes are available at http://cardiogenomics.med.harvard.edu/genes/gene-list. Any SNPs genotyped that were not in Hardy–Weinberg equilibrium (P < 0.01) were not included in the analyses.

Statistical Analyses

Data were presented as means (SDs) or percentages. First, we performed multivariable linear regression models in all 2982 participants to assess the contribution of clinical covariates to the ETT variables, separately for each of the 6 ETT variables. The covariates were selected on the basis of prior studies, and included age, sex, body mass index, diabetes mellitus, smoking, ratio of total to high-density lipoprotein cholesterol, and treatment for hypertension for all ETT variables. Additionally, systolic BP during exercise was also adjusted for systolic BP at rest; diastolic BP during exercise for diastolic BP at rest; HR during exercise for HR at rest; systolic BP during recovery for systolic BP at rest; systolic BP during second stage of exercise, and peak systolic BP during exercise; diastolic BP during recovery for diastolic BP at rest; diastolic BP during second stage of exercise, and peak diastolic BP during exercise; and HR during recovery for HR at rest, HR during second stage of exercise, and peak HR during exercise. Standardized residuals (mean 0, SD 1) constructed after covariate-adjustment served as the primary pheno-
type for the heritability, linkage, and association analyses. These analyses were performed with SAS 8.2 (SAS Institute, Cary, NC).

**Heritability Analyses**
Diastolic BP and HR during recovery had skewed distributions and were therefore modeled as Winsorized variables in the heritability and linkage analyses. Heritability estimates for the ETT variables were obtained in 2053 participants (1068 women) from 949 extended families with at least 2 members by variance-components methods with the Sequential Oligogenic Linkage Analysis Routines package (Southwest Foundation for Biomedical Research, San Antonio, Tex). With this approach, maximum-likelihood estimation was applied to a mixed-effects model that incorporated fixed covariate effects, additive genetic effects, and residual error. The additive genetic effects and residual errors were assumed to be normally distributed and to be mutually independent. The analyses were performed with residuals from the multivariable models mentioned above.

**Linkage Analyses**
Multipoint quantitative trait linkage analyses were conducted in the largest 291 families that underwent a 10-cM–density genome scan (1068 individuals, 543 women) with the residuals from multivariable-adjusted models with use of GENEHUNTER software (Ward Systems Group, Inc, Frederick, Md). Linkage was assessed by use of polygenic models that incorporated genetic marker data (ie, identical-by-descent status) and comparison with models that did not incorporate genetic marker information across the chromosome (multipoint analysis). The log (base 10) of the ratio of the likelihoods of the polygenic models (ie, the log-of-the-odds (LOD) score, the traditional measure of genetic linkage) was calculated.

**Association Analyses**
With a general model of inheritance, we constructed multivariable linear regression analyses to test the null-hypothesis that the level of ETT variables did not differ by candidate SNP genotype. With a sample size of 1000 unrelated individuals (accounting for up to 10% missing genotypes) and a significance level 0.01, we had 80% and 90% power to detect a quantitative trait locus that accounted for 1.3% and 1.6% of the residual variance. False discovery rates were calculated for the associations with the lowest nominal probability values to account for multiple testing.

**Secondary Analyses**
In secondary analyses, we performed heritability, linkage, and association analyses with alternative residuals without trait-specific adjustments. These alternative residuals were created with multivariable linear regression models in all 2982 participants, separately for each of the 6 ETT variables, and the covariates included age, sex, body mass index, diabetes mellitus, smoking, ratio of total to high-density lipoprotein cholesterol, and treatment for hypertension for all ETT variables. In further post hoc analyses, we iterated the primary analyses (heritability, linkage, and association analyses) with the original residuals in a subsample with exclusion of individuals with antihypertensive treatment at baseline (n=180).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**
The mean age of the participants was 43 years (range 20 to 70). The clinical characteristics are presented in Table 1.

**ETT Heritability**
Heritability is the proportion of the unexplained phenotypic variance (ie, after covariates were accounted for) explained by additive genetic effects (ie, additive familial effect, because shared early environment cannot be distinguished from pure genetic effect with this family structure). The heritability analyses demonstrated a highly significant genetic component for all ETT traits. The highest estimates were found for HR, both during exercise and during recovery after exercise, with respective heritability estimates of 0.32 and 0.34 (Table 2). The heritability estimates for systolic and diastolic BP during exercise were higher (0.25 and 0.26) than those for systolic and diastolic BP during the recovery phase (0.16 and 0.13).

**Linkage Analyses**
The linkage analyses resulted in several LOD scores >1.5 (Table 3). Of these only 2 genomic segments reached a level of suggestive linkage (LOD=2.2) as proposed by Lander and Kruglyak. The first of these peaks was located at 1q43-44 (LOD 2.59) and was linked to systolic BP during recovery phase. The other was located at 4p15.3 (LOD 2.37) and was linked to diastolic BP during recovery phase.

**Associations Between ETT Phenotypes and Candidate Gene SNPs**
Ten associations between the examined SNPs and ETT phenotypes reached a nominal significance level of P<0.01 (Table 4). Eight of the associations included genes encoding adrenergic alpha-receptor proteins. Among 235 SNPs tested for association with ETT responses, the minimum nominal probability value was 0.003. The false discovery rate for that

### Table 1. Baseline Characteristics of the Study Sample (n=2982)

<table>
<thead>
<tr>
<th></th>
<th>Men (n=1396)</th>
<th>Women (n=1586)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>43±10</td>
<td>43±10</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.6±3.5</td>
<td>24.3±4.4</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>43</td>
<td>36</td>
</tr>
<tr>
<td>Total cholesterol/HDL cholesterol ratio</td>
<td>5.1±1.6</td>
<td>3.9±1.3</td>
</tr>
<tr>
<td>Hypertension treatment, %</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Systolic BP at rest, mm Hg</td>
<td>122±17</td>
<td>116±18</td>
</tr>
<tr>
<td>Diastolic BP at rest, mm Hg</td>
<td>79±12</td>
<td>75±11</td>
</tr>
<tr>
<td>HR at rest, bpm</td>
<td>71±11</td>
<td>77±11</td>
</tr>
<tr>
<td>Peak systolic BP during exercise, mm Hg</td>
<td>190±22</td>
<td>163±22</td>
</tr>
<tr>
<td>Peak diastolic BP during exercise, mm Hg</td>
<td>94±13</td>
<td>89±12</td>
</tr>
<tr>
<td>Peak heart rate during exercise, bpm</td>
<td>167±11</td>
<td>166±12</td>
</tr>
<tr>
<td>Systolic BP during exercise, * mm Hg</td>
<td>170±24</td>
<td>154±23</td>
</tr>
<tr>
<td>Diastolic BP during exercise, * mm Hg</td>
<td>87±13</td>
<td>84±13</td>
</tr>
<tr>
<td>HR during exercise, * bpm</td>
<td>125±17</td>
<td>141±18</td>
</tr>
<tr>
<td>Systolic BP during recovery, † mm Hg</td>
<td>146±21</td>
<td>126±18</td>
</tr>
<tr>
<td>Diastolic BP during recovery, † mm Hg</td>
<td>70±17</td>
<td>68±14</td>
</tr>
<tr>
<td>HR during recovery, † bpm</td>
<td>105±13</td>
<td>103±13</td>
</tr>
</tbody>
</table>

Values are means ±SD or percentages. HDL indicates high-density lipoprotein; BP, blood pressure; and HR, heart rate.

*Exercise BP and HR were assessed during the Bruce protocol second stage of exercise.
†Recovery BP and HR were assessed at the third minute of the recovery phase after exercise.

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The association was 99%, if adjusted for all genotype-phenotype association tests performed.

Secondary Analyses
The results from the secondary analyses with alternative residuals without trait-specific covariates are shown in Tables II, III, and IV of the online-only Data Supplement. The heritability estimates were generally higher than those from the primary analyses (online Data Supplement Table II). The linkage analyses that used these alternative residuals resulted in several LOD scores >1.5 (online Data Supplement Table III). The 2 genomic segments that reached a level of suggestive linkage in the primary analyses showed high LOD scores also in these secondary analyses. The highest of these peaks ( locus 1q43-44 for systolic BP during recovery phase), demonstrated a LOD score of 3.47 at the same locus for the corresponding trait (without adjustment for resting and exercise systolic BP). The association analyses that used these alternative residuals duplicated 2 of the associations from the primary analyses (the associations of rs544215 and rs3787441, and HR during exercise) (online Data Supplement Table IV).

When all participants with antihypertensive treatment were excluded, the results from the heritability, linkage, and association analyses that used the original residuals were similar to those of the primary analyses, although the point estimates were generally slightly lower and the probability values slightly higher (data not shown).

Discussion
Principal Findings
In this large community-based study with a familial structure, we examined the genetic determinants of hemodynamic and chro-notropic responses to exercise. We observed moderate heritability for each of 6 ETT traits examined, and we found 2 peaks of

### TABLE 2. Heritability Estimates for the Different ETT Phenotypes (n=2053)*

<table>
<thead>
<tr>
<th>ETT Phenotype†</th>
<th>Heritability (SEM)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP during exercise</td>
<td>0.25 (0.06)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic BP during exercise</td>
<td>0.26 (0.06)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HR during exercise</td>
<td>0.32 (0.06)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic BP during recovery</td>
<td>0.16 (0.06)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diastolic BP during recovery</td>
<td>0.13 (0.06)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HR during recovery</td>
<td>0.34 (0.06)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*The heritability estimates are based on residuals from multivariable models adjusted for age, sex, body mass index, diabetes mellitus, smoking status, ratio of total to high-density lipoprotein cholesterol, and treatment for hypertension for all ETT variables. Additionally, systolic BP during exercise was also adjusted for systolic BP at rest; diastolic BP during exercise for diastolic BP at rest; HR during exercise for heart rate at rest; systolic BP during recovery for systolic BP at rest, systolic BP during second stage of exercise, and peak systolic BP during exercise; diastolic BP during recovery for diastolic BP at rest, diastolic BP during second stage of exercise, and peak diastolic BP during exercise; and HR during recovery for HR at rest, HR during second stage of exercise, and peak HR during exercise. ETT indicates exercise treadmill test.

†For definitions of the phenotypes, see Table 1.

### TABLE 3. Maximum Multipoint LOD Scores >1.5 for the Different ETT Phenotypes (n=1068)

<table>
<thead>
<tr>
<th>ETT Phenotype* and Chromosome Location</th>
<th>Map Distance (cM)</th>
<th>Closest Marker(s)</th>
<th>Multivariate-Adjusted LOD Score†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP during exercise</td>
<td>1q32.1</td>
<td>196.7</td>
<td>AFMA132YC9</td>
</tr>
<tr>
<td></td>
<td>5q13.2</td>
<td>78.8</td>
<td>GATA138B05</td>
</tr>
<tr>
<td></td>
<td>10q23.3</td>
<td>106.0</td>
<td>rs1887922</td>
</tr>
<tr>
<td>Diastolic BP during exercise</td>
<td>19q13.1</td>
<td>50.8</td>
<td>GATA156F11</td>
</tr>
<tr>
<td>HR during exercise</td>
<td>1p32.1-31.1</td>
<td>78.4</td>
<td>GATA165C03/GATA152F05</td>
</tr>
<tr>
<td></td>
<td>5q14.3</td>
<td>99.1</td>
<td>GATA89G08</td>
</tr>
<tr>
<td></td>
<td>7p15.1-14.3</td>
<td>37.6</td>
<td>GGAA3F06/GATA13G11</td>
</tr>
<tr>
<td></td>
<td>7q21.1</td>
<td>81.1</td>
<td>GATA73D10/GATA87D11</td>
</tr>
<tr>
<td></td>
<td>14q24.1</td>
<td>52.4</td>
<td>GGAA4A12</td>
</tr>
<tr>
<td>Systolic BP during recovery</td>
<td>1q43-44</td>
<td>269.9</td>
<td>GATA4A09/AFMC013WC9</td>
</tr>
<tr>
<td></td>
<td>2p12</td>
<td>93.7</td>
<td>GATA71604</td>
</tr>
<tr>
<td>Diastolic BP during recovery</td>
<td>4p15.3</td>
<td>27.8</td>
<td>AFM157XG3/ATT015</td>
</tr>
<tr>
<td></td>
<td>4q28.2</td>
<td>117.1</td>
<td>ATA26B08</td>
</tr>
<tr>
<td>HR during recovery</td>
<td>5q35.3</td>
<td>194.1</td>
<td>164XB8</td>
</tr>
<tr>
<td></td>
<td>21q21.1</td>
<td>0</td>
<td>GATA11C12</td>
</tr>
</tbody>
</table>

*For definitions of the phenotypes, see Table 1.
†LOD scores were calculated from residuals from multivariable models. For covariates included in the models, see Table 2.
suggestive linkage for systolic and diastolic BP during recovery from exercise (LOD 2.6 and 2.4, respectively). In addition, we performed analyses of potential associations between ETT variables and 235 SNPs in 14 candidate genes from the neurohormonal pathways. These genes were selected a priori because the neurohormonal systems are known to be important in the regulation of BP and HR, and because most prior genetic association studies of the same traits have focused on single genes in these pathways. The association analyses rendered nonsignificant results after adjustment for multiple statistical testing. In secondary analyses that used alternative residuals without adjustments for trait-specific covariates (such as HR at rest, HR during second stage of exercise, and peak HR during exercise for the HR during recovery trait), the heritability estimates were generally higher, and the linkage peaks from the primary analyses were reproduced, whereas only 2 of the associations from the association analyses were duplicated. The fact that the results differed somewhat between these analyses was expected because exercise response phenotypes adjusted for corresponding resting and exercise covariates are physiologically and genetically different phenotypes from those without adjustment for corresponding covariates. Without adjustment for these trait-specific covariates, the analyses are more influenced by the resting phenotypes (for exercise phenotypes) and resting and exercise phenotypes (for recovery phenotypes).

**Previous Studies of Genetic Determinants of Exercise Hemodynamics**

The HERITAGE family study has previously reported on the genetic determinants of response to exercise.17 Some impor-
tant differences exist between the HERITAGE family study and the present investigation. First, the overall objective of the HERITAGE study was to examine responses to 20 weeks of aerobic exercise training in subjects from a selected sample of sedentary but healthy individuals without hypertension or chronic disease, whereas the present study examined the genetic determinants of response to exercise in a cross-sectional community-based study without any interventions. Second, the HERITAGE study used an exercise protocol with cycle ergometry and hemodynamic measurements at different loads and different percentages of maximal oxygen uptake, whereas we performed ETT with the standardized and widely used Bruce protocol. Third, with 2982 participants, the present study was larger than the HERITAGE study (n = 762). Fourth, the study participants in the HERITAGE study were selected to have a sedentary lifestyle, whereas the participants in the present study were selected from the community. Fifth, whereas the measurements in the HERITAGE study were done in a steady state, the 3-minute steps of the Bruce protocol used in the present study are likely not sufficient to reach true steady state.

Heritability of Hemodynamic Response to Exercise
Our study demonstrated the heritability of hemodynamic response to exercise to be significant, which supports efforts to search for genetic factors that influence ETT traits. The HERITAGE study has reported the heritability for maximal oxygen uptake to be ~50%-55 and that the heritability for training response after 20 weeks of training is ~30% for HR and lower for BP response.36 Further, the heritability estimates for systolic BP, diastolic BP, and HR during submaximal exercise at 50W have been reported as 45%, 55%, and 59%, respectively, in the HERITAGE study. These data have not been published to date but were summarized in another report by the same group of investigators.36 Also, other studies have demonstrated a significant genetic component in hemodynamic and chronotropic response to exercise,37,38 although none of these studies have reported heritability estimates. To our knowledge, estimations of heritability of hemodynamic responses to exercise with a standard Bruce protocol have not been published.

Notably, the 2 highest linkage peaks were found for the 2 traits with the lowest heritability, systolic and diastolic BP during recovery. This might seem contradictory at first glance, but one should remember that these traits are polygenic, which means that many quantitative trait loci of modest effect exist, which contribute to the genetic variability of the traits, and that the linkage analyses does not necessarily pick up signals from all of these.

Genetic Linkage of ETT Phenotypes
We are aware of only 1 previous study that examined genetic linkage of exercise hemodynamics, and that was also a report from the HERITAGE family study.18 The only locus that reached the level of suggestive linkage in this study was detected on chromosome 8q21 (LOD 2.36) for systolic BP training response (ie, the difference in systolic BP at 50W load before and after 20 weeks of training). Additionally, some evidence of linkage was detected on 10q23-24 (LOD 1.84) for systolic BP during exercise (ie, systolic BP at 80% of maximum oxygen uptake). This peak for systolic BP during exercise was supported by the findings in the present study. Even though the LOD score of 1.61 at the same locus did not reach the level of suggestive linkage, this might still be interesting because it is a replication of a finding from the only previous linkage study on hemodynamic response to exercise. One gene in this region that merits further consideration is the retinol binding protein 4 (RBP4) gene, which recently has been associated with insulin resistance in repeated studies.39,40

The highest LOD score in our study was found for systolic BP during the recovery phase at locus 1q43–44. A potential candidate gene in this region is the CHRM3 (acetylcholine receptor M3) gene. Acetylcholine receptors play an important role in the regulation of the cardiovascular system through vagal mediation of the autonomic nervous system. Another acetylcholine receptor subtype, CHRM2, has recently been suggested to be associated with HR recovery after exercise.23

Association Studies of Candidate Genes and ETT Phenotypes
Many of the previous studies that examined associations between candidate genes and hemodynamic response to exercise have focused on individual SNPs in 1 or a limited number of candidate genes,19–22,24,25 These studies have rendered different results, which in part can be explained by the use of small and selected samples. In contrast, the present study is based on a large community-based cohort with unsellected participants from the community. We comprehensively characterized the underlying genetic variation in 14 candidate genes in a reference sample, selected tag SNPs to capture common variation, and genotyped tag SNPs in the Framingham Heart Study cohort. Notably, most of the associations with the lowest nominal probability values were found for SNPs from genes that code adrenergic alpha-receptor proteins. Most previous genetic associations studies of hemodynamic and chronotropic response to exercise have examined genes from the renin-angiotensin-aldosterone19,20,24,25 or β-adrenergic21,22 systems. To our knowledge, no previous studies have been conducted of genes that code adrenergic alpha-receptor proteins in relation to exercise physiology. However, a recently published study demonstrated genetic variation in the ADRA1A gene to be associated with essential hypertension in a Chinese population.41 Nevertheless, although some nominal probability values in the present study were low, no findings resulted that were statistically significant after adjustment for multiple statistical testing. Testing in additional samples will be required to validate these putative associations.

Strengths and Limitations
The strengths of the present study are the large community-based sample, routine assessment of the ETT, and the use of standardized clinical covariates in multivariable models. Further strengths include the simultaneous consideration of heritability, genetic linkage and genetic association in the same study, and the comprehensive characterization of common variation in each examined gene. The present study also
has some limitations. First, because our sample consisted mainly of whites of European descent, the generalizability of our findings to other ethnic groups is unknown. Second, we may have failed to detect SNP-phenotype associations because of insufficient statistical power.

Conclusions

In summary, in our large community-based cohort we found modest heritability for several exercise responses. Further, we found evidence suggestive of genetic linkage to select loci for systolic and diastolic BP during recovery from exercise. Finally, comprehensive analyses of potential associations between ETT variables and 235 SNPs in 14 candidate genes from the neurohormonal pathways rendered results that were nonsignificant after adjustment for multiple testing. However, our findings indicate that the genes that code adrenergic alpha-receptor proteins might be plausible targets for future candidate gene-based studies. Alternatively, genetic mapping by newer approaches such as genome-wide association may yield novel insights into the physiological response to exercise.

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Disclosures

None.

References


The blood pressure and heart rate responses to exercise treadmill testing predict incidence of cardiovascular disease, but the genetic determinants of hemodynamic and chronotropic responses to exercise are largely unknown. The present study demonstrated that blood pressure and heart rate responses to exercise were moderately heritable. Furthermore, we found suggestive genetic linkage for systolic blood pressure during recovery from exercise at chromosome 1 and for diastolic blood pressure during recovery from exercise at chromosome 4. Finally, comprehensive analyses of potential associations between exercise response and 235 single-nucleotide polymorphisms in 14 candidate genes from the neurohormonal pathways rendered results that were nonsignificant after adjustment for multiple testing. However, our findings indicate that the genes that code adrenergic alpha-receptor proteins might be plausible targets for future candidate gene-based studies. Alternatively, genetic mapping with newer approaches such as genome-wide association may yield novel insights into the physiological response to exercise.
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