Exercise Training-Induced Blood Pressure and Plasma Lipid Improvements in Hypertensives May Be Genotype Dependent

James M. Hagberg, Robert E. Ferrell, Donald R. Dengel, Kenneth R. Wilund

Abstract—Exercise training improves cardiovascular disease risk, but individual responses are highly variable. We hypothesized that common polymorphic gene variations would affect these responses. Sedentary obese hypertensive older men who had undergone exercise training were typed at the apolipoprotein (apo) E, angiotensin-converting enzyme (ACE), and lipoprotein lipase (LPL) loci. Individuals of all genotype subgroups were generally similar before training; they also changed body weight, body composition, and VO2max similarly with training. ACE insertion/deletion (ID) genotype individuals (n=10) tended to reduce systolic blood pressure more with training than deletion/deletion (DD) individuals (n=8) (−10 versus −5 mm Hg, P=0.16). ACE II and ID individuals decreased diastolic blood pressure more with training than DD individuals (−10 versus −1 mm Hg, P<0.005). Systolic blood pressure reductions with training were also larger in apoE3 and E4 (n=15) than apoE2 men (n=3) (−10 versus 0 mm Hg, P<0.05). The same trend was evident for diastolic blood pressure (−7 versus −3 mm Hg), but the difference was not significant. Systolic (14 versus −6 mm Hg, P=0.08) and diastolic (−9 versus −5 mm Hg, P=0.10) blood pressure reductions tended to be greater in LPL PvuII +/+ (n=4) than +/− and −/− individuals (n=14). Systolic (−10 versus 3 mm Hg, P<0.05) and diastolic (−9 versus 2 mm Hg, P<0.05) blood pressure reductions were larger in LPL HindIII +/+ and +/− (n=15) than −/− persons (n=3), respectively. LPL PvuII −/− individuals (n=3) had larger increases in HDL cholesterol (11 versus 2 mg/dL, P<0.05) and HDL2 cholesterol (8 versus 0 mg/dL, P<0.05) than LPL PvuII +/+ and +/− individuals (n=15). These results are consistent with the possibility that apoE, ACE, and LPL genotypes may identify hypertensives who will improve blood pressure, lipoprotein lipids, and cardiovascular disease risk the most with exercise training. (Hypertension. 1999;34:18-23.)

Key Words: lipoproteins, HDL cholesterol ♦ genotype ♦ angiotensin-converting enzyme ♦ apolipoproteins E ♦ lipoprotein lipase

A number of reviews have concluded that most but not all hypertensives reduce their blood pressure (BP) significantly with exercise training. It currently is not possible to predict which patients will reduce their BP with exercise training. BP clearly has a genetic basis. Recent evidence indicates that a number of polymorphic gene variations may be more prevalent in hypertensives. A common angiotensin-converting enzyme (ACE) variant has been studied extensively relative to cardiovascular (CV) disease. ACE genotype has been shown to affect left ventricular (LV) mass changes occurring with exercise training. In another recent study, apolipoprotein (apo) E genotype was related to diet-induced BP reductions. These authors proposed that this effect might be the result of a different relationship between plasma cholesterol levels and vascular smooth muscle reactivity in the different apoE genotype groups. Exercise training also generally improves plasma lipid levels, but individual responses are highly variable. Such variable responses to exercise training and the fact that BP and lipid levels are partially genetically determined led us to postulate that genetic polymorphisms may interact with exercise training to differentially affect these variables. This study sought to test the hypothesis that polymorphic variations at the ACE, apoE, and lipoprotein lipase (LPL) gene loci would affect the improvements in BP and plasma lipoprotein lipids resulting from endurance exercise training.

Methods

This was a retrospective study of subjects in a previous study from our laboratory. Subjects provided written consent to participate in the original and follow-up studies. The original study was approved by the University of Maryland–College Park and the University of Maryland at Baltimore School of Medicine Institutional Review Board.
boards. The follow-up study was also approved by these institutions and the University of Pittsburgh Institutional Review boards. DNA was isolated from venous blood through standard methods. Subjects were genotyped for insertion/insertion (II), insertion/deletion (ID), and deletion/deletion (DD) genotypes at the ACE gene locus. DNA samples from control subjects whose ACE genotype was known from direct DNA sequencing were run in each assay for direct comparison to test samples. Subjects also were typed for variations at the apoE locus; subjects with ≥1 apoE2 allele were classified as E2, those with ≥1 apoE4 allele were classified as E4, and all others had only E3 alleles and were classified as E3. Subjects also were typed for the PvuII and HindIII restriction site polymorphisms at the LPL gene locus.

Eighteen men who were sedentary, obese, and hypertensive at the start of the original study served as subjects. These volunteers from the general population underwent laboratory chemistry and maximal exercise testing to ensure that they had no evidence of CV or any other diseases contraindicating vigorous exercise training. Subjects were first instructed on the AHA step I diet (50% to 55% calories from carbohydrate, 30% to 35% from fat, and 15% to 20% from protein; 300 to 350 mg/d cholesterol; and 3 g/d sodium). This diet was maintained throughout the study, with adherence assessed weekly by registered dietitians. After the AHA diet was maintained for ≥8 weeks, blood samples were drawn after a 12-hour overnight fast to assess plasma lipid levels. After training, samples were drawn 24 to 36 hours after the subject’s last exercise. Lipid levels at baseline and after the intervention are the average of 2 samples drawn on different days, all while the subjects were provided with a weight-maintaining AHA step I diet. Plasma triglycerides (TG) and cholesterol were measured enzymatically (Abbott ABA Series 200 bichromatic analyzer, Abbott Laboratories). HDL cholesterol (HDL-C) was measured in the supernatant after precipitation of apoB-containing lipoproteins. A second precipitation was used to separate HDL2-C and HDL3-C. LDL-C was calculated with the Friedewald equation.

Subjects also underwent 4 weeks of weekly measurements before and after training to assess BP, which was the average of 3 values taken on each of these days. BP was measured according to JNC V guidelines; all BP values were measured >24 to 36 hours after any prior exercise test or exercise training session. All subjects initially had a 140 to 179 mm Hg systolic or a 90 to 109 mm Hg diastolic BP. Body composition was assessed by underwater weighing. Waist-to-hip ratio was measured as an index of regional fat distribution. Body fat composition was assessed by underwater weighing.12 Waist-to-hip ratio was measured as an index of regional fat distribution. Subjects also had their V̇O max measured during additional treadmill exercise tests.

Subjects were then randomly assigned to 9 months of exercise with or without weight loss. Exercise training consisted of 3 sessions per week, with intensity and duration progressively increased so that subjects completed 40 minutes of exercise per session at 75% to 85% of VO2max for the last 3 months of training. The weight loss program decreased each subject’s food intake by 300 to 500 kcal/d. Subjects were weight stabilized for 4 weeks before testing after their intervention. Weight loss was similar in the different genotype groups, indicating a comparable number of subjects who underwent exercise training with and without weight loss in all genotype groups. Furthermore, we5 and others9 have shown that exercise training with or without weight loss results in the same BP reduction in persons with high-normal to elevated blood pressure.

Results are presented as mean±SE. Because initial values and training-induced BP changes were similar in the ACE II and ID genotype groups, statistical analyses compared the combined ACE II+ID group (n=10) to the DD genotype group (n=8). Initial values and training BP responses of apoE3 and E4 men were similar; thus, statistical analyses for apoE genotype compared the combined apoE3+E4 (n=15) to the E2 genotype group (n=3). We previously reported the relationship between apoE genotype and plasma lipid changes with exercise training in a larger group that included the subjects in this study.14 Initial values and training-induced BP changes were similar in the LPL PvuII−/− and +/+ genotype groups, and statistical analyses compared the combined LPL PvuII−/− and +/+ (n=14) to the +/+ genotype group (n=4). Initial values and training-induced lipid changes were similar in the LPL PvuII−/− and +/+ groups; thus, these statistical analyses compared the combined LPL PvuII−/− and +/+ (n=15) to the −/− genotype group (n=3). Initial values and exercise training BP responses of LPL HindIII+/− and +/+ men were similar; thus, statistical analyses compared the combined LPL HindIII+/− and +/+ (n=15) to the −/− genotype group (n=3). Independent t tests were used to compare initial values and responses to exercise training between genotype groups. Paired t tests were used to assess the significance of exercise training–induced changes in all variables within genotype groups. A value of P<0.05 was accepted as statistically significant.

Results

ACE genotype and BP changes are shown in Table 1. Initially, ACE II+ID and DD genotype groups had similar ages, body weights, body compositions, and V̇O max. Initial systolic BPs also were similar in these ACE genotype groups. The ACE DD group had a slightly lower initial diastolic BP than the ACE II+ID group. With training, both ACE genotype groups reduced body weights, body fat compositions, and waist-to-hip ratios and increased V̇O max generally significantly and to the same extent. Both systolic and diastolic BPs decreased significantly with training in the ACE

| Table 1. Initial Values and BP Changes in Response to Exercise Training for the Two ACE Genotype Groups |
|-------------|-----------------|-----------------|
| Variable    | ACE Genotype Group |
|             | II+ID (n=10)     | DD (n=8)        |
| Age, y      | 60±2            | 63±2            |
| Weight, kg  | 97.7±4.9        | 90.4±3.9        |
| Initial     | −3.8±1.3†       | −3.9±1.8†       |
| Body fat, % | 33.6±1.5        | 30.6±1.5        |
| Change with training | −2.8±1.1†       | −4.1±1.2†       |
| Waist-to-hip ratio, units | 0.98±0.02       | 0.95±0.02       |
| Change with training | −0.02±0.02      | −0.03±0.01†     |
| V̇O max, mL · kg⁻¹ · min⁻¹ | 25.4±1.8       | 27.3±1.3       |
| Initial     | 3.6±0.6†        | 3.8±0.7†        |
| Change with training | −10±31‡        | −5±3‡          |
| Systolic BP, mm Hg | 156±4          | 152±3          |
| Initial     | 96±2*           | 90±2            |
| Change with training | −10±21§        | −1±2           |

Values are expressed as mean±SE. Change with training values are calculated as final minus initial value; thus, a positive result indicates an increase with exercise training and a negative result indicates a decrease.

*pChange with exercise training significant within group (P<0.05).
†Change with exercise training different between genotype groups (P<0.005).
‡Change with exercise training different between genotype groups (P<0.0005).
§Change with exercise training different between genotype groups (P<0.005).
Initial ages, body weights, body compositions, VO$_2$ max, and VO$_2$ max changes with training were also generally significant in both genotype groups. Body weight, body fat, waist-to-hip ratio, systolic and diastolic BPs were similar in the 2 apoE groups. However, in the apoE3 group, whereas the ACE DD group decreased systolic BP significantly with exercise training twice as much as the ACE DD group, although this difference was not significant ($P=0.16$). However, the diastolic BP reduction with training was significantly greater in the ACE II+ID than in the DD group.

ACE genotype and lipoprotein lipid changes are not shown. All ACE genotype groups were generally similar before training in terms of plasma lipoprotein lipid levels. Individuals with the ACE ID genotype tended to decrease total cholesterol, LDL-C, and TG somewhat less and increase HDL-C and HDL$_2$-C levels somewhat more with exercise training, but none of these differences was significant.

ApoE genotype and BP changes are given in Table 2. Initial ages, body weights, body compositions, VO$_2$ max, and systolic and diastolic BPs were similar in the 2 apoE genotype groups. Body weight, body fat, waist-to-hip ratio, and VO$_2$ max changes with training were also generally significant in both apoE groups and did not differ between apoE groups. However, in the apoE3+E4 men, reductions in both systolic and diastolic BPs with training were significant, whereas neither change was significant in the apoE2 men. In addition, the systolic BP reduction with training was significantly greater in the apoE3+E4 compared with the apoE2 group. Diastolic BP reductions with training were also twice as large in the apoE3+E4 than in the apoE2 group, but this difference was not significant.

LPL HindIII genotype and BP changes are shown in Table 3. The LPL HindIII genotype groups initially had similar ages, body weights, percent body fat, waist-to-hip ratios, VO$_2$ max, and systolic BPs. However, diastolic BP was higher in the combined LPL HindIII than in the DD group.

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ApoE genotype and BP changes are given in Table 2. Initial ages, body weights, body compositions, VO$_2$ max, and systolic and diastolic BPs were similar in the 2 apoE genotype groups. Body weight, body fat, waist-to-hip ratio, and VO$_2$ max changes with training were also generally significant in both apoE groups and did not differ between apoE groups. However, in the apoE3+E4 men, reductions in both systolic and diastolic BPs with training were significant, whereas neither change was significant in the apoE2 men. In addition, the systolic BP reduction with training was significantly greater in the apoE3+E4 compared with the apoE2 group. Diastolic BP reductions with training were also twice as large in the apoE3+E4 than in the apoE2 group, but this difference was not significant.

LPL HindIII genotype and BP changes are shown in Table 3. The LPL HindIII genotype groups initially had similar ages, body weights, percent body fat, waist-to-hip ratios, VO$_2$ max, and systolic BPs. However, diastolic BP was higher in the combined LPL HindIII than in the DD group.

ACE genotype and lipoprotein lipid changes are not shown. All ACE genotype groups were generally similar before training in terms of plasma lipoprotein lipid levels. Individuals with the ACE ID genotype tended to decrease total cholesterol, LDL-C, and TG somewhat less and increase HDL-C and HDL$_2$-C levels somewhat more with exercise training, but none of these differences was significant.

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LPL HindIII genotype and BP changes are shown in Table 3. The LPL HindIII genotype groups initially had similar ages, body weights, percent body fat, waist-to-hip ratios, VO$_2$ max, and systolic BPs. However, diastolic BP was higher in the combined LPL HindIII than in the DD group.

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LPL HindIII genotype and BP changes are shown in Table 3. The LPL HindIII genotype groups initially had similar ages, body weights, percent body fat, waist-to-hip ratios, VO$_2$ max, and systolic BPs. However, diastolic BP was higher in the combined LPL HindIII than in the DD group.

ACE genotype and lipoprotein lipid changes are not shown. All ACE genotype groups were generally similar before training in terms of plasma lipoprotein lipid levels. Individuals with the ACE ID genotype tended to decrease total cholesterol, LDL-C, and TG somewhat less and increase HDL-C and HDL$_2$-C levels somewhat more with exercise training, but none of these differences was significant.
TABLE 4. Initial Values and BP Changes With Exercise Training for LPL PvuII Genotype Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>LPL PvuII Genotype Group</th>
<th></th>
<th></th>
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</thead>
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<tr>
<td></td>
<td>−/− and +/+ (n = 14)</td>
<td>+/+ (n = 4)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>64 ± 1*</td>
<td>57 ± 3</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>97.2 ± 4.1</td>
<td>95.5 ± 8.1</td>
<td></td>
</tr>
<tr>
<td>Change with training</td>
<td>−3.8 ± 1.1†</td>
<td>−6.2 ± 1.0††</td>
<td></td>
</tr>
<tr>
<td>Body fat, %</td>
<td>32.5 ± 1.4</td>
<td>33.1 ± 1.8</td>
<td></td>
</tr>
<tr>
<td>Change with training</td>
<td>−3.1 ± 1.0†</td>
<td>−4.5 ± 0.6†</td>
<td></td>
</tr>
<tr>
<td>Waist-to-hip ratio, units</td>
<td>0.96 ± 0.01</td>
<td>0.99 ± 0.03</td>
<td></td>
</tr>
<tr>
<td>Change with training</td>
<td>−0.01 ± 0.01</td>
<td>−0.04 ± 0.02‡</td>
<td></td>
</tr>
<tr>
<td>VO(_2)max, mL kg(^{-1}) min(^{-1})</td>
<td>25.2 ± 1.4</td>
<td>25.1 ± 1.9</td>
<td></td>
</tr>
<tr>
<td>Change with training</td>
<td>3.7 ± 0.5†</td>
<td>4.5 ± 0.6†</td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>155 ± 3</td>
<td>156 ± 6</td>
<td></td>
</tr>
<tr>
<td>Change with training</td>
<td>−6 ± 2†</td>
<td>−14 ± 5‡</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>95 ± 2</td>
<td>97 ± 4</td>
<td></td>
</tr>
<tr>
<td>Change with training</td>
<td>−5 ± 2†</td>
<td>−9 ± 4‡</td>
<td></td>
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</tbody>
</table>

Values are expressed as mean±SE. Change with training values calculated as in Table 1.

*Difference in initial values between genotype groups (P<0.05).
†Change with exercise training significant within group (P<0.05).
‡Change with exercise training between genotype groups (P=0.05 to 0.10).

The +/− genotype group. With training, the LPL PvuII genotype groups reduced body fat and increased VO\(_2\)max to the same degree. However, the LPL PvuII +/+ group tended to decrease body weight and waist-to-hip ratio to a greater extent than the combined +/− and −/− LPL PvuII group. Both LPL Pvu11I genotype groups decreased systolic and diastolic BPs significantly with training. However, the systolic and diastolic BP reductions with training tended to be greater in the LPL PvuII +/+ than in the combined +/− and −/− genotype group (both P=0.05 to 0.10).

LPL PvuII genotype and lipoprotein-lipid changes are given in Table 5. Initially, the LPL PvuII genotype groups (+/− and +/+ versus −/−) had similar ages, weights, waist-to-hip ratios, VO\(_2\)max, and plasma lipoprotein lipid profiles. However, the combined +/− and +/+ group had greater percent body fat than the −/− group. The 2 LPL PvuII genotype groups also had similar training-induced body weight, body fat, and waist-to-hip ratio changes. However, the combined LPL PvuII +/− and +/+ genotype group increased their VO\(_2\)max nearly twice as much with training as the −/− genotype group. The 2 LPL PvuII genotype groups had similar reductions in total cholesterol, LDL-C, and TG levels with training. However, the HDL-C increase with training was nearly four times greater in the LPL PvuII −/− than in the combined +/− and +/+ group. Furthermore, the combined LPL PvuII +/− and +/+ genotype group did not increase HDL-C levels with training, whereas the −/− men increased HDL-C by 8.5 mg/dL.

### Discussion

In a number of previous reviews, we have concluded that the reduction in BP elicited with exercise training is quite variable, with about 75% of hypertensives decreasing systolic and diastolic BPs significantly and about 25% eliciting no changes in BP. A number of physiological variables have been proposed to differentiate hypertensive BP responders from nonresponders, but these variables generally have minimal predic-
tive capacities. The present data provide some evidence to support the possibility that ACE, apoE, and LPL PvuII and HindIII genotypes may identify hypertensives likely to reduce BP the most with exercise training. Furthermore, the present results indicate that LPL PvuII genotype, along with our previous findings relative to the apoE gene locus, may identify older hypertensive men likely to improve their plasma lipoprotein lipid profiles with exercise training.

These results indicate that ACE genotype affected the reduction in systolic and diastolic BPs elicited with exercise training. ACE II+ID, II+II, and ID genotype men tended to decrease systolic BP more than ACE DD individuals. However, the ACE II+ID genotype men clearly decreased diastolic BP more than ACE DD genotype men. ApoE genotype had more of an impact on the change in systolic BP with exercise training, with apoE3 and E4 men decreasing systolic BP substantially more than apoE2 individuals. The change in diastolic BP with exercise training also tended to be larger in the apoE3 and E4 genotype men compared with the apoE2 genotype men. LPL PvuII+/+ genotype men tended to decrease systolic and diastolic BPs more than LPL PvuII−/− and +/- genotype men. However, LPL HindIII−/− genotype men decreased both systolic and diastolic BPs substantially more than LPL HindIII+/− and +/- genotype men. Because of the limited sample size in this study, it was not possible to statistically determine the independent effects of these 4 different gene markers on BP reductions in hypertensives with exercise training. However, it does appear that LPL HindIII genotype may provide the most information relative to BP reductions with exercise training because it identifies hypertensive men who will reduce both systolic and diastolic BPs with exercise training and the differences in exercise training–induced BP reductions were the largest between LPL HindIII genotypes.

Individuals with the ACE DD genotype are at higher risk for developing CV pathologies, such as CV disease, sudden death, and LV hypertrophy, than ACE ID or II genotype persons. The present data indicate that these high-CV-disease-risk ACE DD individuals appear not to reduce their CV disease risk in terms of BP as much with exercise training as persons with the lower-risk ACE ID and II genotypes. Conversely, apoE3 and E4 individuals have a greater CV disease risk than those with the apoE2 genotype, and our data indicate that these high-risk individuals appear to reduce their CV disease risk in terms of BP the most with exercise training.

Montgomery and coworkers recently reported that ACE genotype had a substantial impact on the increase in LV mass that occurred in young men during military basic training. Their ACE II genotype men did not increase LV mass with a 10-week exercise training program, whereas ID and DD genotype men increased LV mass by 38.5 and 42.3 g, respectively. The renin-angiotensin system, in which ACE plays a critical role, affects arteriolar smooth muscle proliferation and LV cardiac muscle hypertrophy. Thus, it is possible that ACE genotype may have interacted with exercise training in the men in the present study to differentially affect peripheral arteriolar smooth muscle, as well as LV cardiac muscle, structure, and function. However, we have no data in our hypertensive men to assess any underlying CV or renin-angiotensin system mechanisms that might have been responsible for the different BP reductions with exercise training in the 2 ACE genotype groups.

In a recent study, apoE genotype was found to significantly affect the BP reduction that occurred with the institution of a low-fat diet in middle-aged men and women with normal to high-normal BP. In that study, systolic BP decreased significantly more (−6 versus −1 mm Hg) in apoE3 than E4 men and women. A similar difference was evident for diastolic BP reductions between apoE3 and E4 individuals (−5 versus −1 mm Hg). No apoE2 individuals were included in that study. The differential change in BP was attributed to a genotype-dependent interaction with the change in dietary fat intake because sodium intake was kept constant. These investigators proposed that endothelial function might have been affected differentially by the low-fat diet between the apoE genotype groups. However, they, as we, have no physiological evidence of any potential mechanisms underlying the differential BP responses of the apoE genotype groups.

Prolonged endurance exercise training generally improves plasma lipoprotein lipid profiles. However, the increases in plasma HDL-C and HDL2-C with exercise training are highly variable among individuals. Even though Williams et al. reported an average HDL-C increase of 4.2 mg/dL in middle-aged men with 1 year of exercise training, the individual responses ranged from a 20-mg/dL increase to an 8-mg/dL decrease in HDL-C. Furthermore, 9 of these 46 men actually decreased and another 8 did not change HDL-C levels with exercise training. HDL2-C changes with exercise training ranged from an 18-mg/dL increase to a 5-mg/dL decrease, with 9 of the 46 men decreasing and another 15 eliciting no change in HDL2-C levels. Such highly variable responses to a standardized exercise training intervention and the fact that polymorphic variations at a number of gene loci affect plasma lipoprotein lipid levels raise the possibility that specific genotypes may interact with exercise training to affect plasma lipoprotein lipid levels.

Polymorphic variations at a number of key gene loci affect plasma lipoprotein lipid levels. We have previously shown that PvuII and HindIII polymorphic variations at the LPL gene locus affect plasma lipoprotein lipid levels. Previously, we and others have shown that apoE genotype also affects an individual’s plasma lipoprotein lipid profile. We recently reported that apoE genotype has a substantial effect on the changes in plasma HDL-C and HDL2-C elicited with exercise training. In that study, of 51 obese sedentary middle-aged and older men, apoE2 genotype men increased plasma HDL-C levels by 8.2 mg/dL, with 9 months of training, whereas apoE3 and E4 men increased plasma HDL-C levels by 2.7 and 2.0 mg/dL, respectively (both P<0.01 compared with apoE2 men). The same trend was evident for plasma HDL2-C increases with exercise training, with the changes being 5.0, 0.7, and −0.6 mg/dL in the apoE2, E3, and E4 genotype groups, respectively (P<0.01 for both apoE3 and E4 compared with apoE2 men). The 18 men in the present study were part of that study population. In the present study, the changes in plasma HDL-C and HDL2-C
with exercise training in the LPL \textit{PvuII} \textit{−/−} genotype group were substantially greater than those evident in LPL \textit{PvuII} \textit{+/+} and \textit{+/−} genotype men. The present results raise the possibility that LPL \textit{PvuII} genotype also affects the change in lipid levels resulting from exercise training in older men. Furthermore, it appears that LPL \textit{PvuII} genotype may subdivide individuals into groups that have more widely divergent HDL-C and HDL\textsubscript{2}-C responses to exercise training than apoE genotype.

One limitation of this study is the small number of subjects, because most studies assessing independent or interactive genetic effects have substantially larger sample sizes. However, a number of design features of this study lend support for the validity of these results despite the small sample size. Probably the most important feature is the longitudinal study design. Assessing the actual changes resulting from exercise training within an individual accounts for possible baseline differences between genotype groups and individuals that cannot be accounted for in cross-sectional studies. Second, the subjects were relatively homogeneous in terms of age, sex, body composition, health status, and BP. Third, the intervention was standardized across subjects. Furthermore, the intervention duration ensured that subjects had been subjected to an exercise training stimulus sufficient to elicit substantial CV and metabolic adaptations. Finally, diets were standardized, thereby eliminating any possible gene-diet or exercise training–diet interactions that could obscure the gene–exercise training interaction. Optimizing the study design with all of these features may have allowed gene-exercise training interactive effects on BP and plasma lipoprotein lipids to be uncovered despite the small number of subjects. However, we cannot rule out the possibility of a type II statistical error. Another possible interpretation of these results is that they represent genotype-dependent differential changes in CV disease risk factors in response to weight loss. However, we think this is unlikely because very few studies have reported these magnitudes of BP and plasma lipoprotein lipid changes as a result of the rather minimal weight losses experienced by any of the genotype subgroups.

Thus, it appears that ACE, apoE, and LPL \textit{PvuI} and \textit{HindIII} genotypes may identify hypertensive individuals who will reduce BP and thereby reduce their CV disease risk the most with exercise training. LPL \textit{PvuII} genotype may also identify hypertensive individuals who improve HDL-C and HDL\textsubscript{2}-C levels the most with exercise training. Such genotype-dependent responses may eventually allow a better understanding of the mechanisms by which endurance exercise training improves BP and plasma lipoprotein lipid levels. Furthermore, if these candidate markers are replicated in larger trials, they would offer a low-cost means by which to optimally stratify persons at high risk for CV disease to endurance exercise training programs to improve their BP and plasma lipoprotein lipid levels, thereby reducing their CV disease risk.

Acknowledgments

The original research was supported by grants to J.M.H. from the Maryland Affiliate of the American Heart Association and the VA Regional Advisory Group. D.R.D. was supported by NIH National Research Service Award AG-05555. This project was also supported by the Baltimore Veterans Administration GRECC. R.E.F. was supported by NIH grants HL-39107 and HL-45778.

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Hypertension. 1999;34:18-23
doi: 10.1161/01.HYP.34.1.18

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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