Associations of resting heart rate with concentrations of lipoprotein subfractions in sedentary men

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ABSTRACT In major prospective studies it has been reported that high heart rate at rest predicts the development of coronary heart disease (CHD) or cardiovascular disease (CVD) in men, but the mechanisms producing these relationships are unknown. Since lipoprotein levels contribute strongly to the risk of CHD and CVD, we examined the relationship of resting heart rate to plasma concentrations of high-density (HDL), low-density (LDL), and very low-density (VLDL) lipoproteins, apolipoprotein (apo) A-I and A-II, and serum concentrations of lipoprotein subfractions in 81 men to determine if atherogenic lipoproteins could potentially induce the reported association of heart rate with development of CHD or CVD. The significant (p ≤ .05) Spearman’s correlations for resting heart rate vs HDL mass (r = −.24), HDL mass (r = −.40), HDL cholesterol (r = −.36), apo A-I (r = −.29), triglycerides (r = .31), VLDL cholesterol (r = .24), VLDL mass (r = .27), and LDL mass of Sf-0–7 subfraction (r = .30) lend support to our hypothesis of lipoprotein-induced relationships of CHD with heart rate. The correlations for resting heart rate vs triglycerides, HDL cholesterol, HDL mass, VLDL mass, and LDL mass of Sf-0–7 subfraction remain significant when adjusted for adiposity, age, smoking habits, diet, and physical fitness as measured by maximum aerobic power (VO₂ max) or submaximal heart rate during a graded exercise test.


Seven major prospective studies have found high heart rates in men at rest to be predictive of the future manifestation of coronary heart disease (CHD) or cardiovascular disease (CVD): (1) the Chicago Peoples Gas Company Study, a 15 year follow-up of 1233 white men,1 (2) the Chicago Western Electric Company Study, a 17 year follow-up of 1899 white men,1 (3) the Chicago Heart Association Detection Project, a 5 year follow-up of 5784 white men,1 (4) the Glosstrup Population Study, a 10 year follow-up of 436 Danish men,2 (5) the Israeli Ischemic Heart Disease Project,3 a 5 year follow-up of 9764 Israeli men, (6) the Kaiser-Permanent Case-Control Study of 431 sudden cardiac deaths occurring over a 2 year period,4 and (7) the Framingham Study accumulation of 26,030 man-years of follow-up data on men.5 It is not known why men with high resting heart rates are at risk of CHD and CVD. The increased incidences of CHD and CVD are not simply the result of high heart rates in older men, since resting heart rate decreases with age,6,7 but may be a direct result of decreased cardiovascular efficiency or the extra accumulation of vessel wall stress from the additional number of pulse waves.8,9 High heart rates may also be related secondarily to CHD through other risk factors such as blood pressure,1,6 cigarette smoking,1,10 exercise,7,11 or cholesterol level.12

Much evidence suggests that high-density (HDL), low-density (LDL), and very low-density (VLDL) lipoproteins and their subfractions have different relationships to CHD risk. High serum concentrations of HDL cholesterol,13 apolipoprotein (apo) A-I,14 and total lipoprotein mass of HDL15 appear to protect against
CHD. HDL may be divided into two subfractions, a less dense, lipid-enriched HDL, and a more dense protein-enriched HDL, and there is evidence associating low concentrations of both HDL and LDL with CHD risk and severity of the disease. Two studies have compared the level of coronary disease with levels of HDL subfractions in cross-sectional samples of men who underwent coronary arteriography. Miller et al. found degree of stenosis to correlate inversely with concentrations of HDL cholesterol, but not to those of HDL, cholesterol in plasma, and Levy et al. reported that the number of severely diseased coronary arteries correlated with serum concentrations of HDL, mass, but not HDL, mass, as measured by analytic ultracentrifugation. Ballantyne et al. found that survivors of myocardial infarction had less HDL total mass, HDL, cholesterol, HDL, phospholipid, HDL, protein, and HDL, apo A-I than did apparently healthy case-control subjects. In the only prospective study to measure HDL and HDL, that we are aware of, low serum concentrations of both HDL and HDL, mass were found to significantly predict development of CHD.

Less is known about the association of low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) subfractions with CHD. High serum concentrations of total LDL mass with flotation rates (S90) 0–12 were reported to correlate with the number of severely diseased coronary arteries and to predict the occurrence of myocardial infarctions prospectively in men, and the VLDL masses of S90 20–100 and S90 100–400 were found to be predictive of myocardial infarction in the Framingham Study. Women have, on average, less LDL cholesterol, less LDL mass of S90 0–7 (designated in this report as smaller LDL), less intermediate-density lipoprotein (IDL) mass of S90 12–20, less VLDL cholesterol and VLDL mass of S90 20–400, and more HDL, mass and LDL mass of S90 7–12 (henceforth referred to as larger LDL) than men. Some or all of these differences in lipoprotein levels may contribute to the lower incidence of CHD in women as compared with men.

This report examines the associations of resting heart rate with concentrations of lipoproteins and their subfractions in sedentary middle-aged men. From previously reported associations between lipoproteins and CHD, and from the correlations we have observed between lipoprotein concentrations and resting heart rate, we hypothesize that the relationship between resting heart rate and CHD may be mediated in part by CHD-related lipoproteins. Moreover, the associations between resting heart rate and CHD-related lipoprotein concentrations do not appear to be the consequence of physical fitness as measured by maximal aerobic power (VO2 max) or submaximal heart rate during a graded exercise test.

Methods

Subjects. This report concentrates on the baseline measurements of resting heart rate, treadmill performance, and serum and plasma lipoprotein concentrations in 81 sedentary, middle-aged men who later participated in a 1 year exercise trial. The subjects were selected to be free of known cardiovascular disease or abnormalities, acute illness, and active chronic systemic disease, and none used medication likely to interfere with their lipid metabolism or resting heart rates. We also required that all participants have resting blood pressures below 160/100 mm Hg, body weight less than 140% of Metropolitan’s “ideal” weight, plasma levels of total cholesterol below 300 mg/dl, and plasma triglyceride concentrations below 500 mg/dl. None of the subjects had physically strenuous jobs or exercised regularly three or more times per week, and all subjects had normal sinus rhythm.

Laboratory measurements. Subjects reported to our clinic in the morning, having abstained for 12 to 16 hr from all food and from any vigorous activity. Venous blood samples were drawn in Vacutainer tubes providing 1.5 mg/dl disodium EDTA and into empty serum tubes while the subject remained in a sitting position. Plasma and serum were prepared from blood within 2 hr, and the blood, serum, and plasma were all kept at 4°C. Plasma lipid and lipoprotein cholesterol concentrations were determined by the methods of the Lipid Research Clinics. The measurement remained “standardized” according to Lipid Research Clinic criteria during all analyses. The concentrations of HDL and HDL, in serum (as total mass) were determined by the Donner Laboratory of Medical Physics, University of California at Berkeley, by computer analysis of the results of analytic ultracentrifugation. This technique generates a “schlieren curve,” which describes the distribution of lipoproteins according to their high-density flotation (F) and low density flotation (S90) rates, from which concentrations of lipoprotein classes are calculated with the use of the areas under the curve for arbitrarily specified flotation intervals. These include the total lipoprotein mass concentrations of the following S90 intervals: 20–400 (VLDL), 12–20 (IDL), 7–12 (larger LDL), and 0–7 (smaller LDL). For the present analysis, HDL, mass was approximated as the sum of flotation intervals F1, 3.5–9.0 and HDL, mass was approximated as the sum of flotation intervals F1, 0–3.5. Levels of A-I24 and A-II25 were determined in total plasma samples by radial immunodiffusion.

Body density was determined by hydrostatic weighing, and relative body fat was computed according to the equation of Siri. Treadmill tests. Resting heart rates were determined from resting electrocardiograms (ECG) obtained after subjects had rested 3 min in a supine position. All subjects then performed graded exercise tests to exhaustion. The test protocol began with a 3.0 mph walk at 0% grade for minutes 1 and 2 and was then changed to a 6.0 mph run at 0% grade for minutes 3 and 4. The grade during minutes 5 and 6 was 2.5% and was increased 2.5% every minute thereafter, while the speed remained at 6.0 mph. During the exercise test, the ECG was constantly monitored and was recorded at each workload and at peak exercise. Heart rates after 3 min of exercise were obtained from the ECG. Oxygen uptake was determined each minute with a semiautomated metabolic analysis system that has been previously described. The gas analyzers were calibrated before and after each test with room air and a standard mixed gas that had been previously...
analyzed by the micro-Scholander technique. VO_2 max was defined as the peak value calculated during the last 2 min of exercise.

**Dietary assessment.** Three day food records were completed on consecutive days that were randomly assigned so as to ensure a proportional number of week- and weekend days. A trained nutritionist reviewed the written records and if they were unclear verified them with the participants. Records were coded according to the Nutrition Coding Center (Minneapolis) codebook and rules. Mean total caloric and nutrient intakes over the 3 days were determined with use of the computerized food composition tables (version 6 plus) of the Nutrition Coding Center and an analysis program.

**Statistics.** Spearman’s correlation coefficients (r_s) are used to assess all pairwise associations of lipoprotein subfractions, treadmill performance, and supine resting heart rate presented in tables 1 and 2 and the text. Spearman’s rho provides a nonparametric test of significant association, has high efficiency when the data are from a bivariate normal distribution, and is generally robust to extreme or “outlying” observations.

Table 3 presents the associations between resting heart rate and lipoprotein concentrations by partial correlations adjusted for age, percent body fat, cigarettes per day, alcohol intake, and other dietary factors. Because the assumption of multivariate normality may not hold for our data, the standard significance levels and confidence intervals for partial correlations were verified by permutation tests and bootstrap resampling procedures, respectively. To determine a nonparametric significance level, adjusted heart rate and lipoprotein concentrations were obtained from separate regression equations with age, percent body fat, cigarettes per day, and percent calories from alcohol, fat, and carbohydrates as their independent variables. We then randomly permuted, 1000 times, the adjusted heart rates among the adjusted lipoprotein concentrations to obtain 1000 partial correlation coefficients under the null hypothesis of zero partial correlation. A two-tailed nonparametric significance level for testing whether the observed partial correlation was different from zero was then obtained by doubling the proportion of times that the correlations for the permuted data were more extreme than the partial correlation for the original data. To determine a nonparametric 95% confidence interval for a partial correlation coefficient, we constructed 1000 “bootstrapped” data sets by sampling n vector-valued observations (i.e., the elements of the vector for each subject consisting of heart rate, lipoprotein concentrations, and the adjustment variables) with replacement from the original n vector observations, where n is the number of subjects in the sample. One thousand partial correlations were calculated for the 1000 bootstrapped samples, and the correlations were arranged in ascending order. The twenty-fifth and nine hundred seventy-fifth largest partial correlations define a nonparametric 95% confidence interval.

The partial correlations listed in table 3 measure association in terms of beats per minute of heart rate and milligrams per deciliter of lipoprotein concentration and therefore cannot be directly compared with the Spearman correlations listed in table 1, which measure association from the ranks of the observations. Therefore, table 3 also contains unadjusted (Pearson’s) correlation coefficients for the purposes of comparison with the partial correlations.

**Results**

**Subject characteristics.** The men were middle-aged (mean ± SD: 45.7 ± 6.7 years), and for the most part nonsmokers (64 nonsmokers, 17 smokers who smoked an average of 15 cigarettes per day), who ate typical American diets (2485 ± 586 Kcal/day; 40.5 ± 6.7% from fat, 38.1 ± 8.1% from carbohydrates, 15.8 ± 2.5% from protein, and the remaining 5.6 ± 5.9% from alcohol). Since the men selected for study were sedentary and not obese or hyperlipoproteinemic, the group’s average percent body fat (21.6 ± 5.6%) and plasma concentrations of cholesterol (213.9 ± 30.7 mg/dl) and triglycerides (119.3 ± 55.6 mg/dl) were probably different from those of the male population of

| TABLE 1 | Spearman correlation coefficients for supine resting heart rate, treadmill test submaximal heart rate, and VO_2 max vs concentrations of lipoprotein components in middle-aged sedentary men |
|---|---|---|---|---|
| Mean ± SD levels (mg/dl) | Supine resting heart rate | Heart rate after 3 min of exercise | VO_2 max |
| Total cholesterol | 213.9 ± 30.7 | .10 | .20 | .03 |
| Triglycerides | 119.3 ± 55.6 | .31^b | .18 | -.14 |
| HDL cholesterol | 48.6 ± 8.8 | -.36^c | -.15 | .25^a |
| HDL mass (F_1,10 0-9.0) | 271.5 ± 55.6 | -.39^c | -.03 | .24^a |
| HDL_2 mass (F_1,10 3.5-9.0) | 39.9 ± 31.3 | -.24^a | -.08 | .14 |
| HDL_3 mass (F_1,10 0-3.5) | 231.6 ± 36.8 | -.40^c | -.01 | .27^a |
| Apo A-I | 128.8 ± 15.8 | -.29^a | .02 | .08 |
| Apo A-II | 37.1 ± 5.0 | -.10 | -.04 | -.04 |
| LDL cholesterol | 146.0 ± 27.2 | .18 | .19 | .00 |
| Smaller LDL mass (S_1^0 0-7) | 227.8 ± 65.3 | .30^b | .23^a | -.08 |
| Larger LDL mass (S_2^7-12) | 132.3 ± 41.9 | -.15 | .14 | -.04 |
| IDL mass (S_2^12-20) | 42.2 ± 18.8 | .04 | .12 | .01 |
| VLDL cholesterol | 19.3 ± 11.2 | .24^a | .23^a | -.14 |
| VLDL mass (S_2^20-400) | 101.1 ± 68.2 | .27^a | .14 | -.16 |

Sample sizes are n = 81 for mean lipid and lipoprotein concentrations and for the correlations involving supine resting heart rate, n = 80 for correlations involving heart rate after 3 min of exercise, and n = 77 for correlations involving VO_2 max.

Significance levels: ^p ≤ .05, ^p ≤ .01, ^p ≤ .001.
TABLE 2
Spearman correlation coefficients between supine resting heart rate and treadmill test submaximal heart rates and VO2 max in sedentary middle-aged men

<table>
<thead>
<tr>
<th></th>
<th>Supine resting heart rate</th>
<th>Heart rate after 3 min of exercise</th>
<th>VO2 max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting supine heart rate</td>
<td>—</td>
<td>.48c</td>
<td>—</td>
</tr>
<tr>
<td>Heart rate after 3 min of exercise</td>
<td>.48c</td>
<td>—</td>
<td>—.19</td>
</tr>
<tr>
<td>Maximum aerobic power</td>
<td>—</td>
<td>—.19</td>
<td>—.29b</td>
</tr>
</tbody>
</table>

Significance levels: *p ≤ .05; **p ≤ .01; ***p ≤ .0001.

Stanford University employees. The men were habitually sedentary, as evidenced by their relatively high heart rates after 3 min of exercise testing (121.7 ± 13.3 beats/min), low aerobic power (VO2 max of 34.9 ± 6.3 ml/kg/min), and the short duration of their treadmill tests (8.7 ± 1.5 min). The men had resting heart rates that ranged from 40 to 105 beats/min, and the average (±SD) was 68.4 ± 11.4 beats/min for the group. This distribution of resting heart rate is similar to that reported for the Glostrup population,2 and tends to be somewhat lower than the distribution reported for the Chicago,1 Israeli,3 Kaiser,4 and Framingham5 stud-

TABLE 3
Unadjusted and adjusted Pearson correlation coefficients for supine resting heart rate vs lipid and lipoprotein concentrations in sedentary middle-aged men

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted^</th>
<th>These factors only^</th>
<th>These factors plus VO2 max^</th>
<th>These factors plus heart rate after 3 min exercise^</th>
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<tr>
<td>Total triglycerides</td>
<td>.29</td>
<td>.31</td>
<td>.28</td>
<td>.26</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>(.00,.58)</td>
<td>(.04,.57)</td>
<td>(.02,.55)</td>
<td>(.02,.51)</td>
</tr>
<tr>
<td>Significance</td>
<td>.018</td>
<td>.008</td>
<td>.024</td>
<td>.008</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>−.38</td>
<td>−.32</td>
<td>−.24</td>
<td>−.30</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>(.−.55,.−.17)</td>
<td>(.−.51,.−.08)</td>
<td>(.−.44,.−.01)</td>
<td>(.−.51,.−.06)</td>
</tr>
<tr>
<td>Significance</td>
<td>.002</td>
<td>.000</td>
<td>.014</td>
<td>.006</td>
</tr>
<tr>
<td>HDL mass (F1,30 0–9)</td>
<td>−.40</td>
<td>−.40</td>
<td>−.30</td>
<td>−.39</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>(.−.56,.−.23)</td>
<td>(.−.56,.−.15)</td>
<td>(.−.48,.−.05)</td>
<td>(.−.57,.−.17)</td>
</tr>
<tr>
<td>Significance</td>
<td>.002</td>
<td>.002</td>
<td>.008</td>
<td>.002</td>
</tr>
<tr>
<td>HDL2 mass (F1,30 3.5–9)</td>
<td>−.32</td>
<td>−.27</td>
<td>−.17</td>
<td>−.28</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>(.−.53,.−.06)</td>
<td>(.−.50,.−.01)</td>
<td>(.−.38,.−.08)</td>
<td>(.−.49,.−.03)</td>
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<tr>
<td>Significance</td>
<td>.010</td>
<td>.022</td>
<td>.124</td>
<td>.020</td>
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<tr>
<td>HDL3 mass (F1,30 0–3.5)</td>
<td>−.33</td>
<td>−.35</td>
<td>−.30</td>
<td>−.38</td>
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<tr>
<td>95% confidence interval</td>
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<td>(.−.53,.−.12)</td>
<td>(.−.52,.−.01)</td>
<td>(.−.57,.−.14)</td>
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<tr>
<td>Significance</td>
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<td>.004</td>
<td>.014</td>
<td>.002</td>
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<tr>
<td>Apo A-1</td>
<td>−.27</td>
<td>−.22</td>
<td>−.14</td>
<td>−.25</td>
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<tr>
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<td>(.−.42,.−.00)</td>
<td>(.−.34,.−.09)</td>
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<td>Significance</td>
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<td>.066</td>
<td>.236</td>
<td>.024</td>
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<tr>
<td>Smaller LDL mass (S0–7)</td>
<td>.33</td>
<td>.31</td>
<td>.29</td>
<td>.27</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>(.10,.51)</td>
<td>(.09,.49)</td>
<td>(.06,.49)</td>
<td>(.04,.48)</td>
</tr>
<tr>
<td>Significance</td>
<td>.010</td>
<td>.004</td>
<td>.006</td>
<td>.010</td>
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<tr>
<td>VLDL cholesterol</td>
<td>.27</td>
<td>.26</td>
<td>.23</td>
<td>.18</td>
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<tr>
<td>95% confidence interval</td>
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<td>(.−.04,.−.50)</td>
<td>(.−.08,.−.52)</td>
<td>(.−.07,.−.44)</td>
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<td>Significance</td>
<td>.020</td>
<td>.018</td>
<td>.052</td>
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<td>VLDL mass (S1 20–400)</td>
<td>.34</td>
<td>.32</td>
<td>.31</td>
<td>.29</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>(.05,.56)</td>
<td>(.01,.56)</td>
<td>(.02,.54)</td>
<td>(.02,.53)</td>
</tr>
<tr>
<td>Significance</td>
<td>.002</td>
<td>.000</td>
<td>.010</td>
<td>.012</td>
</tr>
</tbody>
</table>

^Calculated for the 77 men for whom complete data were available for % body fat, age, diet, alcohol intake, cigarettes/day, and submaximal heart rate.

^Calculated for the 73 men for whom complete data for VO2 max as well as the other adjustment variables were available.
ies. Means and SDs of lipoprotein concentrations for the group are presented in table 1.

Resting heart rate correlated negatively with the percent of total calories from alcohol ($r_s = -0.27$, $p \leq 0.02$), but it did not correlate significantly with age ($r_s = -0.08$), cigarettes per day ($r_s = 0.15$), coffee intake ($r_s = 0.04$), or percent of total calories from protein ($r_s = 0.11$), fat ($r_s = 0.10$), or carbohydrates ($r_s = 0.07$). Resting heart rate and lipoprotein concentrations were both unrelated to presence of type A personality as assessed by a structured interview,32 hostility (Cook-Medley hostility scale),33 anxiety (Thurstone activity scale34 and Spielberger trait anxiety inventory),35 or depression (Minnesota multiple personality inventory),36 so these personality variables were not considered further. Pairwise intercorrelations among resting heart rate, submaximal heart rate, and VO$_2$ max appear in table 2.

**HDL concentrations.** Resting heart rate correlated negatively (table 1) with plasma concentrations of HDL cholesterol and apo A-I, serum concentrations of total HDL mass ($F_{1.20}, 0–9$), the traditional estimates of HDL$_{3}$ ($F_{1.20}, 0–3.5$) and HDL$_{2}$ ($F_{1.20}, 3.5–9.0$), and HDL mass of each of the seven individual flotation intervals within $F_{1.20}, 1.5–5.0$ (results for individual flotation intervals not displayed). Much of the association between resting supine heart rate and HDL mass appeared to be due to low serum concentrations of HDL mass in men with supine heart rates above 70 to 75 beats/min. Figure 1, top, displays the average distribution of serum HDL mass concentrations by flotation rates for 54 men in the lower and middle tertiles of heart rate (40 to 73 beats/min) vs the average distribution for the 27 men in the upper tertile (73 to 104 beats/min). The lowest two tertiles were combined because their separate HDL mass distributions were indistinguishable, whereas the average serum HDL mass concentration for those in the upper tertile with respect to heart rate was clearly less than concentrations for those in the lower tertiles over a broad range of flotation intervals. The difference in the average HDL mass concentration in men with low-to-moderate heart rates minus the average for men with high heart rates is displayed in figure 1, bottom.

Table 3 presents the partial correlations between resting heart rate and concentrations of the various HDL parameters while controlling for effects of age, percent of total calories from protein, fat, carbohydrates, and alcohol, percent body fat, and cigarettes per day and the corresponding unadjusted correlations for the 77 men from whom complete dietary information was obtained. Correlations that were significant ($p \leq 0.05$) by the traditional parametric procedure were also significant ($p \leq 0.05$) by the nonparametric permutation test, and usually did not include zero in their 95% confidence interval. The negative correlations for resting heart rate vs HDL cholesterol, HDL$_{2}$ mass, HDL$_{3}$ mass, and total HDL mass all remained significant at $p \leq 0.05$ with these adjustments, but the negative correlation between resting heart rate vs apo A-I was slightly weakened ($p \leq 0.066$) by the adjustment.

Partial correlations were also used to assess whether the significant correlations between resting heart rate and HDL components were mediated by processes associated with the traditional fitness parameters of VO$_2$ max or submaximal heart rate. VO$_2$ max correlated positively (table 1) with concentrations of HDL cholesterol, total serum HDL mass, HDL mass of $F_{1.20}, 0–3.5$ (predominantly HDL$_{1}$), and with the individual flotation intervals within $F_{1.20}, 1.5$ to 3.0. However, since VO$_2$ max was only weakly correlated with resting heart rate ($r_s = -0.20$), the addition of VO$_2$ max to the other adjustment variables slightly weakened but did
not eliminate the significance of the associations of HDL cholesterol and HDL₃ mass with resting heart rate.

**LDL concentrations.** Resting heart rate was positively correlated with serum concentrations of smaller LDL mass (table 1) and with the five individual flotation intervals within Sf 1 to 6, but it did not correlate with other parameters of LDL concentration. The partial correlation for smaller LDL vs resting heart rate was significant when adjusted for age, diet, body fat, cigarette use, and either VO₂ max or submaximal heart rate after 3 min of exercise (table 3).

**VLDL and triglyceride concentrations.** There was a positive correlation between resting heart rate and plasma VLDL cholesterol, serum VLDL mass, and total plasma triglyceride concentrations. Graphic analysis (not displayed) suggested that most of these associations were due to high concentrations of these lipoprotein components in men with resting heart rates above 80 beats/min. All three correlations remained significant when adjustments for age, adiposity, diet, and cigarette use (table 3) were made, and resting heart rate remained correlated (p ≤ .05) with total plasma triglycerides and VLDL mass when VO₂ max was added to the set of adjustment variables. VLDL cholesterol also correlated with heart rate after 3 min of exercise testing (table 1).

**Multiple regression analysis of resting heart rate.** The three lipoprotein subfractions that correlated with resting heart rate also correlated significantly (p ≤ .05) with one another: r₁ = −.27 for HDL mass vs smaller LDL mass, r₂ = −.22 for HDL mass vs VLDL mass, and r₃ = .46 for smaller LDL mass vs VLDL mass. Multiple regression analysis was applied to assess whether lipoprotein subfractions contributed independently to variations in resting heart rate (table 4). Thirty percent of the resting heart rate variance was attributed to a linear combination of total HDL mass, smaller LDL mass, larger LDL mass, IDL mass, and VLDL mass, and significant linearly independent associations were suggested for serum concentrations of HDL mass, smaller LDL mass, IDL mass, and VLDL mass with resting heart rate.

**Discussion**

The association between low resting heart rate and low incidence of CHD is often ascribed to physical fitness, since training decreases heart rate at rest and may also reduce CHD risk. Based on our findings we hypothesize that the increased risk of CHD among men with high resting heart rates could also be the consequence of high-risk lipoprotein profiles. Resting heart rate may have been shown to predict development of CHD to a significant degree in seven prospective studies in part because it serves well as a surrogate variable for CHD-related lipoproteins that were not measured. The discussion that follows speculates on several physiologic mechanisms that could potentially give rise to these observed correlations, examines in the light of our findings the tendency for resting heart rate to become a nonsignificant predictor of CHD or CVD when included with other risk factors in multivariate analysis, and concludes with consideration of the strengths and weaknesses of our analysis and presentation.

**Mechanisms.** The partial correlations listed in table 3 show that the negative correlation between resting heart rate and HDL cholesterol, HDL₃ mass, and total HDL mass and the positive correlation between resting heart rate and smaller LDL mass and VLDL mass could not be solely ascribed to the linear relationships of these variables to percent body fat, age, cigarettes per day, and the percent of total calories from alcohol, protein, fat, or carbohydrates. Although aerobic exercise effectively lowers resting heart rate, triglycerides, smaller LDL mass, and VLDL mass, while increasing total HDL mass and HDL cholesterol, among this sample of middle-aged sedentary men, most of the associations between resting heart rate and levels of these lipoproteins appeared to be independent of physical fitness as measured by either submaximal treadmill heart rates or VO₂ max.

The correlations between resting heart rate and lipoprotein concentrations may in part be the consequence of elevated thyroid hormones in men with rapid resting heart rates. Two specific findings suggest that HDL concentrations are inversely related to levels of thyroid hormones: HDL cholesterol concentrations correlate negatively with thyroxin levels of asymptomatic men, and HDL cholesterol and HDL₃ mass are decreased by hyperthyroidism and increased by hypothyroidism. The positive correlation we ob-

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**TABLE 4**

<table>
<thead>
<tr>
<th>Multiple regression analysis of supine resting heart rate as a function of lipoprotein mass concentrations in 81 middle-aged men</th>
<th>Coefficient</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>74.044</td>
<td></td>
</tr>
<tr>
<td>Total HDL mass (F₁₀₆, 0–9)</td>
<td>−.66</td>
<td>.003</td>
</tr>
<tr>
<td>Smaller LDL mass (Sf₀–7)</td>
<td>.040</td>
<td>.05</td>
</tr>
<tr>
<td>Larger LDL mass (Sf₇–12)</td>
<td>.034</td>
<td>.27</td>
</tr>
<tr>
<td>IDL mass (Sf₁₂–20)</td>
<td>−.188</td>
<td>.02</td>
</tr>
<tr>
<td>VLDL mass (Sf₂₀–400)</td>
<td>.064</td>
<td>.005</td>
</tr>
</tbody>
</table>

Thirty percent of the variance in resting heart rate is explained by the linear model. Serum lipoprotein mass concentrations are mg/100 ml.
served between resting heart rate and smaller LDL mass, however, appears inconsistent with Stri-
sower’s\(^4\) observation that total LDL mass (S \(S^0\) 0–12) is
increased by hypothyroidism and decreased by hy-
perthyroidism. The effect of thyroid status on VLDL
cholesterol or triglycerides is less clear, with studies
showing normal or increased levels in hypothyroid-
ism.\(^4\) Thus, variation in thyroid hormone activity may
contribute to the inverse correlation between resting
heart rate and HDL concentrations, but by itself does
not explain comprehensively the atherogenic lipopro-
tein profile associated with elevated resting heart rate.

The relationships of resting heart rate to HDL and
triglyceride concentrations we observed cross section-
ally in men are the converse of those induced by \(\beta-
blockers\) such as atenolol, metoprolol, propranolol,
and oxprenolol.\(^46\),\(^47\) Whereas we report that
resting heart rate correlates positively with triglyc-
erides and negatively with HDL cholesterol, the
decrease in resting heart rate induced by \(\beta\)-blocking
drugs is accompanied by an increase in plasma tri-
glyceride and a decrease in HDL cholesterol.\(^46\),\(^47\) How-
ever, despite the lower drug-induced heart rate, adre-
nergic blockade increases plasma catecholamine
concentrations\(^48\) and therefore may represent a physio-
logic condition similar to the higher sympathetic activ-
ity in some men with high resting heart rates.\(^49\) Cate-
cholamines appear to inactivate lipoprotein lipase\(^50\) in
vitro, and it has been postulated that reduced lipopro-
tein lipase activity from elevated levels of catechola-
mases may reduce the fractional rate of removal of
endogenous triglycerides and in turn precipitate a fall
in plasma concentrations of HDL cholesterol.\(^46\) Thus,
catecholamines may mediate the relationship between
resting heart rate and lipoprotein patterns.

**Multivariate analysis of heart rate and CVD or CHD.**

Multiple logistic regression is frequently used in an
attempt to identify components of CHD risk that can be
ascribed to the independent effects of individual risk
factors. However, the statistical problem of separating
out that component of CHD risk that is associated with
resting heart rate and independent of other risk factors
is formidable given (1) the correlation of resting heart
rate with other variables in the model and (2) that other
risk factor variables may also serve in concert with
resting heart rate as surrogates for unmeasured vari-
bles. Heart rates could relate to CHD through physical
fitness, lipoprotein profiles, cardiovascular health, or
the combination of several of these factors. In each
case, the coefficient for resting heart rate in a multiple
logistic regression analysis of CHD may become non-
significant when these other risk factors are included in
the regression model. An association between resting
heart rate and CHD produced by physical fitness could
be weakened in a multivariate analysis as a result of
colinearity among heart rate and other important risk
factors. For example, physically active men tend to be
nonsmokers and have lower relative weight and re-
duced cholesterol concentrations in addition to having
low resting heart rate.\(^37\)–\(^40\) An association between rest-
ing heart rate and CHD that is related to levels of
lipoprotein subfractions could be weakened in a multi-
ivariate analysis as a result of the correlations between
lipoprotein subfractions and other risk factors in the
model. For example, in our data we find that smokers
have lower serum concentrations of HDL\(_2\) and HDL\(_3\)
mass than nonsmokers,\(^39\) and that plasma total chole-
sterol level correlates significantly with levels of HDL\(_3\)
mass \(r_s = .23\), smaller LDL mass \(r_s = .64\), VLDL
mass \(r_s = .37\), and VLDL cholesterol \(r_s = .49\). Finally,
the strong correlations for resting heart rate vs
systolic \(r_s = .32\) and diastolic blood pressure \(r_s = .32\)
would obscure a resting heart rate–CHD relation-
ship arising from low cardiovascular efficiency or in-
creased frequency of pulse wave microtrauma\(^8\) when
blood pressure is also included in the regression mod-
el. Therefore, adjustment for age, serum cholesterol,
blood pressure, relative weight, and cigarettes per day
would be expected to weaken the significance of find-
ings regarding prediction of CHD or CVD or occur-
rence of sudden death with resting heart rate as found
in the Chicago Peoples Gas Company Study, the Chi-
cago Western Electric Company Study, the Chicago
Heart Association Detection Project, and the Israeli
and Kaiser-Permanente Studies.

**Parametric vs nonparametric statistical analysis.**
The computer-intensive approach of the bootstrap\(^31\)
and permutation (randomization) tests\(^30\) provides two non-
parametric methods for testing whether the partial cor-
relations listed in table 3 are significantly more ex-
reme than would be expected by chance if adjusted
resting heart rate were unrelated to adjusted lipoprotein
concentrations. Those correlations that were signifi-
cant at \(p \leq .05\) by the traditional parametric approach
that postulates multivariate normality were all signifi-
cant at \(p \leq .05\) by the nonparametric permutation test
that postulates a weaker condition of the adequacy of
the linear adjustment. The consistency of the two ap-
proaches permits great confidence in the results. There
are only three partial correlations for which the boot-
strap includes the value zero in its nonparametric 95% confidence
interval when the traditional parametric
test and the nonparametric permutation test show the
partial correlation to be significantly different than
zero. The discrepancies are minor and involve only those correlations that become nonsignificant by further adjustment. The bootstrap may assign greater stochastic variability to the partial correlations because both the adjustment variables and the variables to be adjusted are resampled from the data and contribute to the estimation error, whereas the adjustment variables are held fixed in the permutation test. Bootstrap estimation of confidence intervals requires further theoretical support and results should therefore be interpreted with caution. Nevertheless, the 95% confidence intervals listed in Table 3 show that the small size of our sample provides limited precision in estimating partial correlations.

Caveats and limitations of our results. The significant associations described in this study were evaluated conservatively via nonparametric rank correlations and partial correlations with the use of distribution-free significance levels. The resting heart rate/lipoprotein correlations therefore do not appear to be the consequence of outlying observations or inappropriate tests of hypotheses. Nevertheless, we emphasize two important caveats. First, not all prospective studies find high resting heart rate to be predictive of CHD or CVD. This may in part result from the fact that some men have low heart rates because of underlying disease of the cardiac conduction system. Bradycardia may also be observed in individuals with hypothyroidism who are at increased risk of CVD. Second, although in this study three complementary statistical procedures all showed resting heart rate to be significantly correlated with an atherogenic profile in sedentary men, we caution that further studies involving larger and more diverse samples are required to precisely estimate the magnitude of the correlations and to establish their generality.

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References


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34. Thurstone LL: Thurstone Temperment Scale. Chicago, 1953, Science Reseach Association

Erratum
In a recently published article by Weksler et al. (Circulation 71: 334, 1985) an author’s name was inadvertently excluded from the list. The list should have read: Babette B. Weksler, M.D., Karen Tack-Goldman, B.A., Valvanur A. Subramanian, M.D., Shreekant V. Karwande, M.D., and William A. Gay, Jr., M.D.