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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 ($p \leq .05$) Spearman's correlations for resting heart rate vs HDL₂ mass ($r_s = -.24$), HDL₃ mass ($r_s = -.40$), HDL cholesterol ($r_s = -.36$), apo A-I ($r_s = -.29$), triglycerides ($r_s = .31$), VLDL cholesterol ($r_s = .24$), VLDL mass ($r_s = .27$), and LDL mass of S_f 0-7 subfraction ($r_s = .30$) lend support to our hypothesis of lipoprotein-induced relationships of CHD with heart rate. The correlations for resting heart rate vs triglycerides, HDL cholesterol, HDL₃ mass, VLDL mass, and LDL mass of S_f 0-7 subfraction remain significant when adjusted for adiposity, age, smoking habits, diet, and physical fitness as measured by maximum aerobic power ($\dot{V}O_2$ max) or submaximal heart rate during a graded exercise test.

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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 Glostrup 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-Permanente 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

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CHD. HDL may be divided into two subfractions,¹⁶⁻¹⁸ a less dense, lipid-enriched HDL₂ subfraction and a more dense protein-enriched HDL₃ subfraction, and there is evidence associating low concentrations of both HDL₂ and HDL₃ 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.*¹⁹ found degree of stenosis to correlate inversely with concentrations of HDL₂ cholesterol, but not to those of HDL₃ cholesterol in plasma, and Levy *et al.*²⁰ reported that the number of severely diseased coronary arteries correlated with serum concentrations of HDL₃ mass, but not HDL₂ mass, as measured by analytic ultracentrifugation. Ballantyne *et al.*²¹ found that survivors of myocardial infarction had less HDL₂ total mass, HDL₂ cholesterol, HDL₂ phospholipid, HDL₂ protein, and HDL₂-apo A-I than did apparently healthy case-control subjects. In the only prospective study¹⁵ to measure HDL₂ and HDL₃ that we are aware of, low serum concentrations of both HDL₂ mass and HDL₃ 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 (S_f^0) 0-12 were reported to correlate with the number of severely diseased coronary arteries²⁰ and to predict the occurrence of myocardial infarctions prospectively¹⁵ in men, and the VLDL masses of S_f^0 20-100 and S_f^0 100-400 were found to be predictive of myocardial infarction in the Framingham Study.¹⁵ Women have, on the average, less LDL cholesterol, less LDL mass of S_f^0 0-7 (designated in this report as smaller LDL), less intermediate-density lipoprotein (IDL) mass of S_f^0 12-20, less VLDL cholesterol and VLDL mass of S_f^0 20-400, and more HDL₂ mass and LDL mass of S_f^0 7-12 (henceforth referred to as larger LDL) than men.¹⁷ 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 ($\dot{V}O_2$ 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.¹¹ 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,²² 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.²³ The measurement remained "standardized" according to Lipid Research Clinic criteria during all analyses. The concentrations of HDL₂ and HDL₃ 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.¹⁶⁻¹⁸ This technique generates a "schlieren curve," which describes the distribution of lipoproteins according to their high-density flotation (F) and low to very-low density flotation (S_f^0) 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 S_f^0 intervals: 20-400 (VLDL), 12-20 (IDL), 7-12 (larger LDL), and 0-7 (smaller LDL). For the present analysis, HDL₂ mass was approximated as the sum of flotation intervals $F_{1,20}$ 3.5-9.0 and HDL₃ mass was approximated as the sum of flotation intervals $F_{1,20}$ 0-3.5.¹⁶ Levels of A-I²⁴ and A-II²⁵ were determined in total plasma samples by radial immunodiffusion.

Body density was determined by hydrostatic weighing,²⁶ and relative body fat was computed according to the equation of Siri.²⁷

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.²⁸ 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.²⁹ $\dot{V}O_2$ 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) code-book 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 tests³⁰ and bootstrap resampling procedures, respectively.³¹ 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.³⁰ 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.³¹

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 \pm 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: $40.5 \pm 6.7\%$ from fat, $38.1 \pm 8.1\%$ from carbohydrates, $15.8 \pm 2.5\%$ from protein, and the remaining $5.6 \pm 5.9\%$ from alcohol). Since the men selected for study were sedentary and not obese or hyperlipoproteinemic, the group's average percent body fat ($21.6 \pm 5.6\%$) 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 $\dot{V}O_2$ max vs concentrations of lipoprotein components in middle-aged sedentary men

	Mean \pm SD levels (mg/dl)	Supine resting heart rate	Heart rate after 3 min of exercise	$\dot{V}O_2$ 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 ($F_{1,20}$ 0-9.0)	271.5 ± 55.6	-.39 ^C	-.03	.24 ^A
HDL ₂ mass ($F_{1,20}$ 3.5-9.0)	39.9 ± 31.3	-.24 ^A	-.08	.14
HDL ₃ mass ($F_{1,20}$ 0-3.5)	231.6 ± 36.8	-.40 ^C	-.01	.27 ^A
Apo A-I	128.8 ± 15.8	-.29 ^B	.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° 0-7)	227.8 ± 65.3	.30 ^B	.23 ^A	-.08
Larger LDL mass (S° 7-12)	132.3 ± 41.9	-.15	.14	-.04
IDL mass (S° 12-20)	42.2 ± 18.8	.04	.12	.01
VLDL cholesterol	19.3 ± 11.2	.24 ^A	.23 ^A	-.14
VLDL mass (S° 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 $\dot{V}O_2$ max.

Significance levels: $^A p \leq .05$, $^B p \leq .01$, $^C p \leq .001$.

TABLE 2**Spearman correlation coefficients between supine resting heart rate and treadmill test submaximal heart rates and $\dot{V}O_2$ max in sedentary middle-aged men**

	Supine resting heart rate	Heart rate after 3 min of exercise	$\dot{V}O_2$ max
Resting supine heart rate	—	.48 ^C	— .19
Heart rate after 3 min of exercise	.48 ^C	—	— .29 ^B
Maximum aerobic power	— .19	— .29 ^B	—

Significance levels: ^Ap ≤ .05; ^Bp ≤ .01; ^Cp ≤ .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 ($\dot{V}O_2$ 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 (\pm 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**

	Unadjusted ^A	Adjusted for % body fat, age, cigarettes/day, alcohol intake, and other dietary factors		
		These factors only ^A	These factors plus $\dot{V}O_2$ max ^B	These factors plus heart rate after 3 min exercise ^A
Total triglycerides	.29	.31	.28	.26
95% confidence interval	(.00, .58)	(.04, .57)	(.02, .55)	(.02, .51)
Significance	.018	.008	.024	.008
HDL cholesterol	— .38	— .32	— .24	— .30
95% confidence interval	(— .55, — .17)	(— .51, — .08)	(— .44, — .01)	(— .51, — .06)
Significance	.002	.000	.014	.006
HDL mass ($F_{1,20}$ 0–9)	— .40	— .40	— .30	— .39
95% confidence interval	(— .56, — .23)	(— .56, — .15)	(— .48, — .05)	(— .57, — .17)
Significance	.002	.002	.008	.002
HDL ₂ mass ($F_{1,20}$ 3.5–9)	— .32	— .27	— .17	— .28
95% confidence interval	(— .53, — .06)	(— .50, .01)	(— .38, .08)	(— .49, — .03)
Significance	.010	.022	.124	.020
HDL ₃ mass ($F_{1,20}$ 0–3.5)	— .33	— .35	— .30	— .38
95% confidence interval	(— .48, — .15)	(— .53, — .12)	(— .52, — .01)	(— .57, — .14)
Significance	.002	.004	.014	.002
Apo A-I	— .27	— .22	— .14	— .25
95% confidence interval	(— .45, — .09)	(— .42, .00)	(— .34, .09)	(— .45, — .04)
Significance	.018	.066	.236	.024
Smaller LDL mass (S_f^0 0–7)	.33	.31	.29	.27
95% confidence interval	(.10, .51)	(.09, .49)	(.06, .49)	(.04, .48)
Significance	.010	.004	.006	.010
VLDL cholesterol	.27	.26	.23	.18
95% confidence interval	(— .02, .50)	(— .04, .50)	(— .08, .52)	(— .07, .44)
Significance	.020	.018	.052	.124
VLDL mass (S_f^0 20–400)	.34	.32	.31	.29
95% confidence interval	(.05, .56)	(.01, .56)	(.02, .54)	(.02, .53)
Significance	.002	.000	.010	.012

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

^BCalculated for the 73 men for whom complete data for $\dot{V}O_2$ 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 ($r_s = -.27$, $p \leq .02$), but it did not correlate significantly with age ($r_s = -.08$), cigarettes per day ($r_s = .15$), coffee intake ($r_s = .04$), or percent of total calories from protein ($r_s = .11$), fat ($r_s = .10$), or carbohydrates ($r_s = .07$). 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 $\dot{V}O_2$ 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

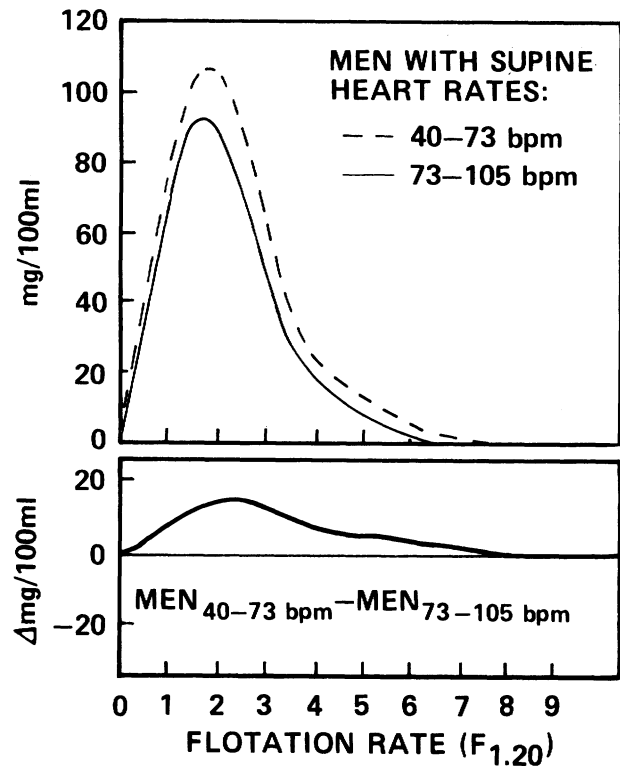


FIGURE 1. *Top*, Distribution of the average serum HDL mass concentration by particle flotation rate for men in the lower and middle tertiles of resting heart rate (40 to 73 beats/min) vs that in men in the upper tertile (73 to 104 beats/min). (The average HDL particle distribution for a group is formed by averaging the heights of the individual curves belonging to the members of each tertile at each flotation rate). *Bottom*, Difference in the average serum HDL mass concentrations for men with low-to-moderate heart rates minus the average for men with high resting heart rates.

$\leq .05$) by the traditional parametric procedure were also significant ($p \leq .05$) 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 $p \leq .05$ with these adjustments, but the negative correlation between resting heart rate vs apo A-I was slightly weakened ($p \leq .066$) 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 $\dot{V}O_2$ max or submaximal heart rate. $\dot{V}O_2$ 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_3), and with the individual flotation intervals within $F_{1.20}$ 1.5 to 3.0. However, since $\dot{V}O_2$ max was only weakly correlated with resting heart rate ($r_s = -.20$), the addition of $\dot{V}O_2$ 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 S_f 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 $\dot{V}O_2$ 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 ($p \leq .05$) with total plasma triglycerides and VLDL mass when $\dot{V}O_2$ 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 ($p \leq .05$) with one another: $r_s = -.27$ for HDL mass vs smaller LDL mass, $r_s = -.22$ for HDL mass vs VLDL mass, and $r_s = .46$ 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,³⁷⁻⁴⁰ 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 $\dot{V}O_2$ 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,^{41, 42} and HDL cholesterol and HDL₂ mass are decreased by hyperthyroidism and increased by hypothyroidism.^{43, 44} The positive correlation we ob-

TABLE 4
Multiple regression analysis of supine resting heart rate as a function of lipoprotein mass concentrations in 81 middle-aged men

	Coefficient	p value
Intercept	74.044	
Total HDL mass (F _{1,20} 0-9)	-.066	.003
Smaller LDL mass (S _f 0-7)	.040	.05
Larger LDL mass (S _f 7-12)	.034	.27
IDL mass (S _f 12-20)	-.188	.02
VLDL mass (S _f 20-400)	.064	.005

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 Strisower's⁴⁴ observation that total LDL mass (S_f 0–12) is increased by hypothyroidism and decreased by hyperthyroidism. The effect of thyroid status on VLDL cholesterol or triglycerides is less clear, with studies showing normal or increased levels in hypothyroidism.⁴⁵ 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 lipoprotein profile associated with elevated resting heart rate.

The relationships of resting heart rate to HDL and triglyceride concentrations we observed cross sectionally in men are the converse of those induced by β -blocking drugs such as atenolol, metoprolol, propranolol, and oxprenolol.^{46, 47} Whereas we report that resting heart rate correlates positively with triglycerides and negatively with HDL cholesterol, the decrease in resting heart rate induced by β -blocking drugs is accompanied by an increase in plasma triglyceride and a decrease in HDL cholesterol.^{46, 47} However, despite the lower drug-induced heart rate, adrenergic blockade increases plasma catecholamine concentrations⁴⁸ and therefore may represent a physiologic condition similar to the higher sympathetic activity in some men with high resting heart rates.⁴⁹ Catecholamines appear to inactivate lipoprotein lipase⁵⁰ in vitro, and it has been postulated that reduced lipoprotein lipase activity from elevated levels of catecholamines 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 variables. 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 nonsignificant 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 reduced cholesterol concentrations in addition to having low resting heart rate.^{37–40} An association between resting heart rate and CHD that is related to levels of lipoprotein subfractions could be weakened in a multivariate 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 HDL₂ and HDL₃ mass than nonsmokers,³⁹ and that plasma total cholesterol level correlates significantly with levels of HDL₃ 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 relationship arising from low cardiovascular efficiency or increased frequency of pulse wave microtrauma^{8, 9} when blood pressure is also included in the regression model. Therefore, adjustment for age, serum cholesterol, blood pressure, relative weight, and cigarettes per day would be expected to weaken the significance of findings regarding prediction of CHD or CVD or occurrence of sudden death with resting heart rate as found in the Chicago Peoples Gas Company Study, the Chicago 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 bootstrap³¹ and permutation (randomization) tests³⁰ provides two nonparametric methods for testing whether the partial correlations listed in table 3 are significantly more extreme than would be expected by chance if adjusted resting heart rate were unrelated to adjusted lipoprotein concentrations. Those correlations that were significant at $p \leq .05$ by the traditional parametric approach that postulates multivariate normality were all significant 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 approaches permits great confidence in the results. There are only three partial correlations for which the bootstrap 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.³¹ 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.^{6, 12, 51, 52} This may in part result from the fact that some men have low heart rates because of underlying disease of the cardiac conduction system.⁵³ Bradycardia may also be observed in individuals with hypothyroidism who are at increased risk of CVD.⁵⁴ 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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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., Shreekanth V. Karwande, M.D., and William A. Gay, Jr., M.D.