

# Association of Triglyceride-to-HDL Cholesterol Ratio With Heart Rate Recovery

MEHDI H. SHISHEBOR, DO<sup>1</sup>  
 BYRON J. HOOGWERF, MD<sup>2</sup>  
 MICHAEL S. LAUER, MD<sup>3</sup>

**OBJECTIVE**— Insulin resistance is associated with autonomic dysfunction. An attenuated decrease in heart rate after exercise (or heart rate recovery [HRR]) predicts all-cause mortality and is believed to reflect decreased parasympathetic activity. Utilizing triglyceride/HDL cholesterol concentration as a marker of insulin resistance, we sought to assess the association between insulin resistance and HRR.

**RESEARCH DESIGN AND METHODS**— Our study population included 4,963 healthy adults who participated in the Lipid Research Clinics Prevalence Study and underwent exercise testing. HRR was considered abnormal if it did not drop  $\geq 42$  bpm 2 min after completion of exercise. Fasting blood specimens were drawn.

**RESULTS**— Individuals in the highest quartile of triglyceride/HDL cholesterol had a significantly higher prevalence of abnormal HRR (40 vs. 30%, multivariable-adjusted prevalence ratio 1.18, 95% CI 1.01–1.39;  $P = 0.04$ ). As a continuous variable, an increase in 1 SD of triglyceride-to-HDL cholesterol ratio was associated with a greater likelihood of an abnormal HRR, even after adjusting for  $>20$  covariates (adjusted OR 1.16, 95% CI 1.07–1.25;  $P < 0.001$ ). During 12 years of follow-up, there were 284 deaths. In age- and sex-adjusted analysis, participants with an abnormal HRR and high triglyceride-to-HDL cholesterol ratio had significantly higher mortality than those with a normal HRR and high triglyceride-to-HDL cholesterol ratio (hazard ratio = 1.49, 95% CI 1.08–2.04;  $P = 0.015$ ).

**CONCLUSIONS**— HRR is associated with triglyceride-to-HDL cholesterol ratio and identifies patients with insulin resistance who are at increased risk of death.

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Insulin resistance and compensatory hyperinsulinemia are associated with increased sympathetic and decreased parasympathetic activity (1). An attenuated decrease in heart rate immediately after exercise (abnormal heart rate recovery [HRR]) is a strong predictor of all-cause mortality and may reflect decreased parasympathetic activity (2). Insulin re-

sistance leads to increased assembly and secretion of triglyceride-rich VLDL and decreased HDL cholesterol (3). Hence, the triglyceride-to-HDL cholesterol ratio is a strong correlate of insulin resistance (3–5). Therefore, we prospectively hypothesized that an association would exist between an abnormal HRR and triglyceride-to-HDL cholesterol concentration

ratio, and that this association might partially account for the increase in mortality noted among otherwise healthy people with elevated triglyceride-to-HDL cholesterol ratio.

## RESEARCH DESIGN AND METHODS

**METHODS**— The study population was derived from the Lipid Research Clinics Prevalence Study, a population-based epidemiological study that has been described in detail elsewhere (6). Briefly, the study was conducted from 1972 to 1976 in the U.S. and Canada to determine the prevalence of dyslipidemia. Of the 60,495 individuals that were screened, 13,852 with certain lipid abnormalities and 15% selected at random were invited for a second visit; among these, 8,681 underwent exercise testing. Participants provided a detailed medical, family, and drug history in addition to questions regarding exercise habits, smoking, alcohol use, educational level, and occupational status. All subjects gave informed consent before entering the study.

Participants in this study included adults aged  $>30$  years who reached stage 2 of the modified Bruce protocol. Participants with a history of diabetes, pregnancy, stroke, coronary heart disease, cardiovascular disease, cardiac arrhythmia, valvular heart disease, and those treated with lipid-lowering medications were excluded.

## Exercise testing

Study subjects underwent exercise testing according to the modified Bruce protocol (7). Participants exercised until they reached 90% of their age- and fitness-predicted maximum heart rate for 1 min. The test was terminated if chest pain, fatigue, leg pain, dyspnea, or electrocardiographic changes were observed. Blood pressure and heart rate were measured immediately after exercise and at 2 min into recovery. HRR was considered abnormal if it did not drop  $\geq 42$  bpm 2 min after completion of exercise.

From the <sup>1</sup>Department of Internal Medicine, The Cleveland Clinic Foundation, Cleveland, Ohio; the <sup>2</sup>Department of Endocrinology, The Cleveland Clinic Foundation, Cleveland, Ohio; and the <sup>3</sup>Department of Cardiology, The Cleveland Clinic Foundation, Cleveland, Ohio.

Address correspondence and reprint requests to Michael S. Lauer, MD, FACC, Director of Clinical Research and Stress Laboratory, Department of Cardiology, Desk F-25, Cleveland, OH 44195. E-mail lauerm@ccf.org.

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**Abbreviations:** HRR, heart rate recovery.

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Table 1—Baseline characteristics according to quartiles of plasma triglyceride-to-HDL cholesterol ratio

Characteristics	<0.66	0.66–1.1	1.1–1.8	> 1.8	P
n	1239	1242	1241	1241	
Age (years)	44 ± 11	45 ± 10	44 ± 10	44 ± 9	0.264
Female sex	810 (65)	549 (44)	394 (32)	193 (16)	<0.001
White ethnicity	1,169 (94)	1,176 (95)	1,204 (97)	1,214 (98)	<0.001
BMI (kg/m <sup>2</sup> )	24 ± 3	25 ± 4	26 ± 4	28 ± 4	<0.001
Resting heart rate (per minute)	81 ± 14	80 ± 13	80 ± 13	81 ± 13	0.350
Resting systolic blood pressure (mmHg)	122 ± 17	125 ± 17	127 ± 17	129 ± 16	<0.001
Vasodilator treatment	42 (3)	57 (5)	66 (5)	80 (6)	0.017
Fasting glucose (mmol/l)	5.2 ± 0.5	5.3 ± 0.5	5.3 ± 0.5	5.5 ± 0.5	<0.001
Cholesterol level (mmol/l)	5.3 ± 1.1	5.6 ± 1.1	5.8 ± 1.1	6.0 ± 1.1	<0.001
Triglycerides (mmol/l)	0.78 ± 0.2	1.2 ± 0.3	1.6 ± 0.4	3.1 ± 1.6	<0.001
HDL cholesterol (mmol/l)	1.7 ± 0.4	1.4 ± 0.3	1.2 ± 0.3	0.9 ± 0.2	<0.001
LDL cholesterol (mmol/l)	3.4 ± 1.0	3.8 ± 1.0	4.0 ± 1.0	3.8 ± 1.1	<0.001
Current smoker	307 (25)	428 (34)	504 (41)	561 (45)	<0.001
Alcohol (g per week)	10 ± 14	11 ± 16	13 ± 19	15 ± 20	<0.001
Exercise at least three times a week	279 (22)	247 (20)	238 (19)	229 (18)	0.063
Regularly engage in strenuous exercise	336 (27)	319 (26)	287 (23)	278 (22)	0.021
Education level (at least some college)	656 (53)	609 (49)	559 (45)	592 (48)	0.001

Data are means ± SD or n (%).

### Determination of fasting plasma lipid and glucose

As described in detail elsewhere, fasting plasma glucose was measured by ferricyanide method in a single-channel autoanalyzer or by the hexokinase method on an ABA-100 (8). Fasting plasma cholesterol and triglyceride levels were determined by Technicon AutoAnalyzer I or Autoanalyzer II. There was an excellent precision for lipid parameters between runs, within runs, and among instruments, as reported earlier (8).

### Follow-up

From 1977, all participants who were examined at visit 2 and were ≥30 years of age were followed for an average of 12 years for all-cause mortality, namely death from any cause, whether cardiovascular or noncardiovascular. There was 99.6% completeness of follow-up for assessment of vital status (9).

### Statistical analysis

Continuous variables are presented as means ± SD. For descriptive purposes, we divided the study population into quartiles according to triglyceride-to-HDL cholesterol concentration ratio. Differences in baseline and exercise characteristics were compared using the Kruskal-Wallis test for continuous variables and the Mantel-Haenszel extension test for categorical variables. Logistic re-

gression analysis was used to assess the impact of potential confounders on the association between plasma triglyceride-to-HDL cholesterol concentration ratio and abnormal HRR.

We used propensity analysis to further assess the association between triglyceride-to-HDL cholesterol concentration ratio and HRR after accounting for multiple confounders. Utilizing the fourth quartile of triglyceride-to-HDL cholesterol concentration ratio as the cut-off point, we divided all individuals into two groups, low triglyceride/HDL cholesterol versus high triglyceride/HDL cholesterol concentration. Utilizing a logistic regression analysis, we generated a propensity score for high triglyceride-to-HDL cholesterol concentration ratio. We considered age, sex, BMI, smoking, resting heart rate, resting systolic blood pressure, antihypertensive treatment, LDL cholesterol, fasting glucose, alcohol consumption, occupational status, educational level, strenuous exercise, and heart rate at stage 2 as a measure of physical fitness (10) for this model. We then matched each subject with high triglyceride-to-HDL cholesterol to one with low triglyceride-to-HDL cholesterol ratio using the derived propensity score. Subsequently, multivariable logistic regression analysis was performed on the propensity-matched group to assess the association between triglyceride/HDL cholesterol and

abnormal HRR. We also examined any interactions between prespecified variables and the association of triglyceride/HDL cholesterol with abnormal HRR.

We also examined triglyceride-to-HDL cholesterol ratio as a continuous variable to further assess its association with abnormal HRR. We tested logarithmic, exponential, and inverse transformations models to find the best-fit model for the association of triglyceride-to-HDL cholesterol ratio and abnormal HRR.

In supplementary analyses, we used Kaplan-Meier curves and Cox proportional hazards modeling to examine the association between triglyceride-to-HDL cholesterol concentration ratio and mortality, accounting for the presence or absence of an abnormal HRR and other confounders. We used the fourth quartile concentration as a cut point to define abnormal triglyceride-to-HDL cholesterol concentration ratio. All analyses were performed using the SAS system version 8.2 (Cary, NC).

**RESULTS**— Of the 8,681 subjects who underwent exercise testing at the second visit, 4,963 met our study criteria. Baseline characteristics according to quartiles of triglyceride/HDL cholesterol concentration are shown in Table 1. Men were more likely to have higher triglyceride-to-HDL cholesterol ratio than women. Individuals in the upper quar-

Table 2—Exercise characteristics of women (1,946) and men (3,017) according to quartiles of plasma triglyceride-to-HDL cholesterol ratio

	<0.66	0.66–1.1	1.1–1.8	>1.8	P
Characteristics of women					
n	810	549	395	192	
Peak workload (metabolic equivalents)*	9.1 ± 2	8.8 ± 2	8.8 ± 2	8.5 ± 2	0.002
HRR (bpm)	52 ± 15	51 ± 15	48 ± 15	46 ± 14	<0.001
Heart rate at stage 2 (bpm)	148 ± 17	149 ± 17	148 ± 17	148 ± 17	0.509
Peak heart rate (bpm)	161 ± 16	160 ± 16	159 ± 15	157 ± 16	<0.001
Peak systolic blood pressure (mmHg)	159 ± 24	163 ± 26	164 ± 28	173 ± 28	<0.001
Abnormal heart rate recovery, n (%)	194 (24)	164 (30)	141 (36)	75 (39)	<0.001
Ischemic ST-segment response, n (%)	33 (4)	26 (5)	17 (4)	8 (4)	0.831
Characteristics of men					
n	429	693	847	1048	
Peak workload (metabolic equivalents)*	11.3 ± 2	11.0 ± 2	10.9 ± 2	10.8 ± 2	<0.001
HRR (bpm)	53 ± 15	49 ± 14	48 ± 14	46 ± 13	<0.001
Heart rate at stage 2 (bpm)	129 ± 17	132 ± 18	133 ± 17	136 ± 17	<0.001
Peak heart rate (bpm)	163 ± 15	162 ± 15	161 ± 16	162 ± 14	0.049
Peak systolic blood pressure (mmHg)	170 ± 28	172 ± 26	172 ± 28	175 ± 29	0.11
Abnormal heart rate recovery, n (%)	99 (23)	277 (33)	277 (33)	417 (40)	<0.001
Ischemic ST-segment response, n (%)	12 (3)	25 (4)	34 (4)	34 (3)	0.950

Data are means ± SD or n (%). \*Metabolic equivalents refer to estimated exercise capacity where 1 metabolic equivalent = 3.5 ml · kg<sup>-1</sup> · min<sup>-1</sup> of oxygen consumption.

tiles of triglyceride-to-HDL cholesterol ratio had higher BMI, higher resting blood pressure, higher glucose, higher total cholesterol, lower LDL cholesterol, lower frequency of exercise, and lower levels of completed education.

Exercise characteristics according to quartiles of triglyceride-to-HDL cholesterol ratio are shown in Table 2. Both men and women in the upper quartiles of triglyceride/HDL cholesterol had a significantly higher prevalence of abnormal HRR. Among men, the heart rate at stage 2 was higher with higher triglyceride-to-HDL cholesterol ratios, implying worse physical fitness; this association was not seen among women.

**Triglyceride-to-HDL cholesterol concentration ratio and HRR**

High triglyceride-to-HDL cholesterol ratio was defined as a value >1.8 (the cut point for the 4th quartile of triglyceride-to-HDL cholesterol ratio). Using this cut point, the prevalence of abnormal HRR was significantly higher in those with elevated triglyceride-to-HDL cholesterol ratio compared with those with low ratio (40 vs. 30%, prevalence ratio 1.34, 95% CI 1.23–1.46; P < 0.001). This association remained statistically significant after adjusting for age, sex, BMI, smoking, resting heart rate, resting systolic blood pressure, antihypertensive treatment, LDL

cholesterol, fasting glucose, alcohol consumption, occupational status, educational level, strenuous exercise, and physical activity (adjusted OR 1.18, 95% CI 1.01–1.39; P = 0.04).

We tested the association between plasma triglyceride-to-HDL cholesterol ratio and abnormal HRR for possible interactions with the prespecified variables of age, sex, race, BMI, resting systolic blood pressure, smoking, LDL cholesterol, regular physical activity, and resting heart rate. No interactions were found.

We also assessed the association of fasting triglyceride-to-HDL cholesterol ratio as a continuous variable with abnormal HRR. We tested three different transformations (logarithmic, exponential, and inverse) of plasma triglyceride-to-HDL cholesterol ratio to predict abnormal HRR. The best model fit was found with the inverse transformation triglyceride-to-HDL cholesterol ratio. An increase in 1 SD of triglyceride-to-HDL cholesterol ratio was associated with an odds ratio (OR) of 1.35 (95% CI 1.26–1.44; P < 0.001) for prediction of an abnormal HRR. This association remained statistically significant after adjusting for age, sex, BMI, smoking, resting heart rate, resting systolic blood pressure, antihypertensive treatment, HDL and LDL cholesterol, triglycerides, fasting glucose, alcohol consumption, occupational status,

educational level, strenuous exercise, and physical activity (adjusted OR 1.16, 95% CI 1.07–1.25; P < 0.001). When we excluded subjects taking antihypertensive medications or with an abnormal ST-segment response, the association was actually stronger (n = 4,477, adjusted OR 1.20, 95% CI 1.11–1.30; P < 0.001).

**Propensity analysis**

A propensity score based on >20 variables was generated for high triglyceride-to-HDL cholesterol ratio (individuals in the fourth quartile). Of the 1,241 patients with high triglyceride-to-HDL cholesterol ratio, we were able to propensity match 911 subjects with those in the low triglyceride-to-HDL cholesterol ratio (individuals in the first to third quartile). The c-statistic for the logistic model was 0.82, indicating good discrimination between the two groups.

There was an excellent match between the two groups for >20 variables, as shown in Table 3. Despite very similar baseline characteristics and propensity scores between two groups, individuals with high triglyceride-to-HDL cholesterol ratio had a higher prevalence of an abnormal HRR (38 vs. 33%, prevalence ratio 1.14, 95% CI 1.01–1.29; P = 0.04). In addition, this association persisted after adjusting for age, sex, BMI, smoking,

**Table 3—Baseline and exercise characteristics in propensity-matched patients**

Characteristics	Low triglyceride/ HDL cholesterol	High triglyceride/ HDL cholesterol
<i>n</i>	911	911
Age (years)	44 ± 9	44 ± 10
Women	178 (20)	178 (20)
White ethnicity	876 (96)	886 (97)
BMI (kg/m <sup>2</sup> )	27 ± 4	27 ± 3
Resting heart rate (bpm)	80 ± 13	80 ± 13
Resting systolic blood pressure (mmHg)	129 ± 16	129 ± 17
Vasodilator treatment	56 (6)	58 (6)
Fasting glucose (mmol/l)	5.5 ± 0.5	5.5 ± 0.5
Cholesterol level (mmol/l)	5.8 ± 1.1	5.8 ± 1.1
LDL cholesterol (mmol/l)	3.9 ± 1.0	3.9 ± 1.0
Current smoker	401 (44)	384 (42)
Alcohol (g per week)	15 ± 19	14 ± 20
Exercise at least three times a week	152 (17)	163 (18)
Regularly engage in strenuous exercise	187 (20)	200 (22)
Education	431 (47)	442 (48)
Blue-collar occupation	303 (33)	290 (32)
Exercise workload (metabolic equivalents)*	10 ± 2	10 ± 2
Heart rate at stage 2 (bpm)	138 ± 19	138 ± 18
Peak heart rate (bpm)	162 ± 15	161 ± 14
Peak systolic blood pressure (mmHg)	173 ± 28	174 ± 28
Ischemic ST-segment response	31 (3)	34 (4)

Data are means ± SD or *n* (%). \*Metabolic equivalents refer to estimated exercise capacity where 1 metabolic equivalent = 3.5 ml · kg<sup>-1</sup> · min<sup>-1</sup> of oxygen consumption.

resting heart rate, resting systolic blood pressure, antihypertensive treatment, HDL and LDL cholesterol, triglycerides, fasting glucose, alcohol consumption, occupational status, educational level, strenuous exercise, and physical activity in the propensity-matched group (adjusted prevalence ratio 1.22, 95% CI 1.01–1.48; *P* = 0.04).

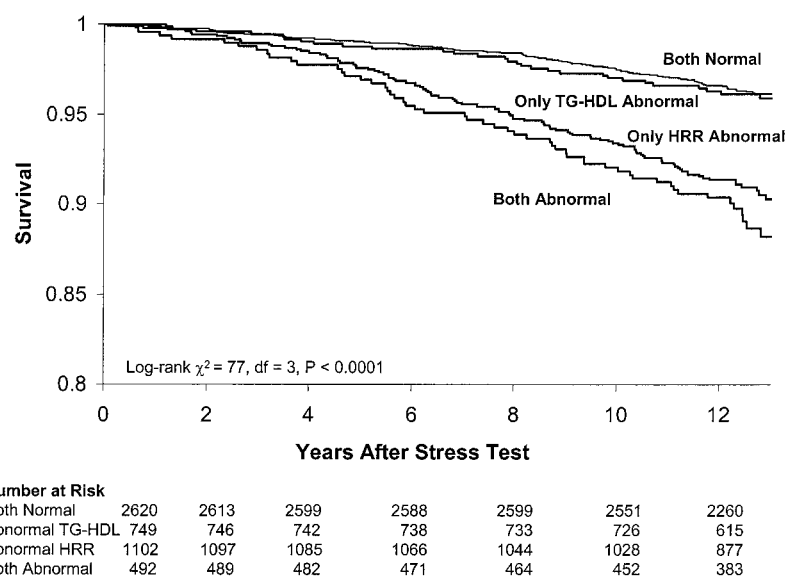
Finally, we assessed the association of triglyceride-to-HDL cholesterol ratio as a continuous variable with HRR in the propensity-matched population. An increase in 1 SD of triglyceride-to-HDL cholesterol ratio was associated with an OR of 1.37 (95% CI 1.18–1.58; *P* < 0.001) for prediction of an abnormal HRR in the propensity-matched group. This association was even stronger after adjusting for age, sex, BMI, smoking, resting heart rate, resting systolic blood pressure, antihypertensive treatment, HDL and LDL cholesterol, triglycerides, fasting glucose, alcohol consumption, occupational status, educational level, strenuous exercise, physical activity, and propensity score in the propensity-matched population (OR 1.38, 95% CI 1.18–1.62; *P* < 0.001).

### Triglyceride-to-HDL cholesterol ratio, HRR, and mortality

During 12 years of follow-up, there were 284 deaths. High triglyceride-to-HDL

cholesterol ratio was associated with a modest increase of all-cause mortality (6.0 vs. 4.9%, unadjusted hazard ratio [HR] = 1.30, 95% CI 1.01–1.68; *P* = 0.04). In age- and sex-adjusted analysis, participants with an abnormal heart recovery and high triglyceride-to-HDL cholesterol ratio had significantly higher mortality than those with a normal HRR and high triglyceride-to-HDL cholesterol ratio (HR = 1.49, 95% CI 1.08–2.04; *P* = 0.015). When we limited our analyses to subjects with an abnormal HRR, the presence of a high triglyceride-to-HDL cholesterol ratio was not predictive of death (age- and sex-adjusted HR = 1.25, 95% CI 0.89–1.76; *P* = 0.20). Hence, an abnormal HRR was predictive of death regardless of the triglyceride-to-HDL cholesterol ratio (Fig. 1).

We also assessed the association of triglyceride-to-HDL cholesterol ratio and all-cause mortality as a continuous variable. An increase in 1 SD of triglyceride-to-HDL cholesterol ratio was associated with all-cause mortality (unadjusted HR = 1.23, 95% CI 1.07–1.41; *P* = 0.003). After adjusting for abnormal HRR, this association was weaker (age- and sex-adjusted HR = 1.15, 95% CI 1.01–1.32; *P* = 0.04), whereas abnormal HRR remained a significant predictor of all-cause mortality (age- and sex-adjusted HR = 2.60, 95% CI 2.05–3.29, *P* < 0.001) (Fig. 1).



**Figure 1—Kaplan-Meier survival curves for abnormal HRR and triglyceride-to-HDL cholesterol ratio. Abnormal triglyceride-to-HDL cholesterol ratio was defined as any value in the fourth quartile. TG-HDL, triglyceride/HDL cholesterol.**

There were 89 subjects who were thought to have died of cardiovascular causes. In a model that included triglyceride/HDL cholesterol, HRR, age, and sex, an increase in 1 SD of triglyceride-to-HDL cholesterol ratio predicted cardiovascular death (adjusted HR = 1.55, 95% CI 1.12–2.13;  $P = 0.008$ ) as did an abnormal HRR (adjusted HR = 2.29, 95% CI 1.47–3.55,  $P < 0.001$ ).

There were no marked interactions noted between sex and either HRR or triglyceride-to-HDL cholesterol ratio for prediction of all-cause mortality or cardiovascular mortality.

**CONCLUSIONS**— The results of the present study suggest that there is a strong association between abnormal HRR and triglyceride-to-HDL cholesterol ratio, even after adjusting for glucose level and other confounding factors. Furthermore, the presence of abnormal HRR in individuals with elevated triglyceride-to-HDL cholesterol ratio is associated with an increased risk of death. Taken together, the present study suggests that abnormal HRR, an easily obtained measure of autonomic function, may identify a group of patients with insulin resistance who have a prognostically important impairment of parasympathetic tone.

Insulin resistance is thought to play a significant role in the pathogenesis of cardiovascular disease and predicts increased morbidity and mortality, perhaps through disturbances of autonomic balance (11,12). Insulin resistance has been associated with decreased parasympathetic nervous system activity, though the biological mechanism linking these two has not been clearly elucidated (13,14).

We utilized abnormal HRR as a measure of autonomic dysfunction. Abnormal HRR, an easily measured tool during routine exercise testing, is an independent predictor of mortality in submaximal and symptom-limited exercise stress testing (2). Although the current study was not designed to link HRR with abnormalities of parasympathetic function, this association has been convincingly demonstrated by Imai et al. (15); this group showed that the initial steep decline in heart rate after exercise can be eliminated by prior administration of atropine. Utilizing abnormal HRR as a measure of autonomic dysfunction and triglyceride-to-HDL cholesterol ratio as a maker of insulin resistance, we now confirm and extend pre-

vious findings linking insulin resistance to autonomic dysfunction in a large population-based study. The presence of abnormal HRR in patients with abnormal triglyceride-to-HDL cholesterol ratio may identify individuals at significantly greater risk of death. The association between abnormal HRR and triglyceride-to-HDL cholesterol ratio were independent of confounding factors such as glucose, BMI, and hypertension. This would indicate that HRR might add important clinical information in individuals with insulin resistance that are independent of traditional risk factors, such as glucose, BMI, or hypertension.

Caution must be taken when interpreting the results of this study since we did not have direct measures of insulin resistance and heart rate variability. Thus, our investigation represents an epidemiological analysis that is balanced on several levels of association. This study only provides a possible link between triglyceride-to-HDL cholesterol ratio, HRR, and insulin resistance, but not a causal relationship. In addition, waist-to-hip measurements were not available in this population and not accounted for in multivariate regression analysis; however, we did adjust for BMI. Furthermore, the reliability of peak heart rate must be questioned because of the submaximal nature of the tests. Of note, only 10% of women, compared with 35% of men, fell into the highest quartile of triglyceride-to-HDL cholesterol ratio. This may be because women have higher HDL cholesterol levels in general and, therefore, raises questions regarding the use of the triglyceride-to-HDL cholesterol ratio as a sole marker of insulin resistance.

It is not known whether HRR, either with or without associated insulin resistance, is a modifiable risk factor. Recent data have suggested that a formal exercise program within Phase II cardiac rehabilitation may improve HRR (16). Very recently Welzig et al. (17) found an intriguing association between administration of statins and improved responsiveness to parasympathetic stimulation.

In conclusion, in this epidemiological analysis, an abnormal HRR is associated with an abnormal triglyceride-to-HDL cholesterol ratio, itself a correlate of insulin resistance. Although an abnormal HRR should not be considered as a measure of insulin resistance, HRR may identify patients with abnormal triglyceride-

to-HDL cholesterol ratio who are at increased risk of death. This easily measured part of routine exercise stress testing should be considered in conjunction with other risk factors that identify patients with insulin resistance such as triglyceride-to-HDL cholesterol ratio. Easier methods of identifying patients with insulin resistance and cardiac autonomic dysfunction may lead to the design and execution of future intervention trials within a clinical setting.

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