Aims Slower heart rate recovery (HRR) following exercise is associated with the metabolic syndrome, yet the temporal relationship between the two remains unknown. We investigated the cross-sectional and longitudinal associations of slower HRR following a graded exercise treadmill test (GXT) with metabolic syndrome components and LDL-C.

Methods and results Participants aged 18–30 from the Coronary Artery Risk Development in Young Adults study underwent a symptom-limited maximal GXT at baseline (n = 4319) and 7 years later. HRR was calculated as the difference between maximum heart rate (HR) and HR 2 min after test cessation. Slower baseline HRR was associated with a higher cross-sectional level but not longitudinal (15 year follow-up) increases in blood pressure, triglyceride, waist circumference, and LDL-C. No cross-sectional or longitudinal association was observed between HRR and HDL-C. In contrast, participants with one or two or more metabolic syndrome components (National Cholesterol Education Program III and American Diabetes Association criterion) at baseline examination had significantly larger longitudinal declines in HRR \([-3.48 \text{ bpm} (P < 0.05)\] and \([-5.64 \text{ bpm} (P < 0.001)\], respectively) from baseline to year 7, when compared with participants without syndrome components \([-2.40 \text{ bpm}\).]

Conclusion Slower HRR does not precede development of the metabolic syndrome, but appears after syndrome components are present.

Introduction Slower heart rate recovery (HRR) following exercise has been linked to the metabolic syndrome and several of its components in cross-sectional studies. \(^{1-5}\) The rapid deceleration of heart rate (HR) immediately following exercise is dependent on a complex interplay between various intrinsic, neural, and humoral factors. However, autonomic nervous system (ANS)-mediated responses, in particular parasympathetic reactivation, are a major determinant of HRR. \(^{6-10}\) Slower HRR may, therefore, be indicative of decreased ANS responsiveness. \(^{11-13}\)

Associations between HRR and the metabolic syndrome are thought to support the hypothesis that an imbalance in the ANS may directly contribute to the development of the metabolic syndrome. \(^1\) However, autonomic dysfunction is also a known complication of diabetes. As temporal relationships cannot be established from cross-sectional analyses, it is not known whether slow HRR is part of a central dysfunction preceding the development of metabolic syndrome components or whether the presence of metabolic syndrome components is associated with decreases in HRR over time.

In the Coronary Artery Risk Development in Young Adults (CARDIA) study, we investigated three aims: (1) whether slower HRR is associated with higher baseline levels of the following: blood pressure, lipids, body mass index (BMI), and waist circumference; (2) whether slower baseline HRR is associated with longitudinal increases in blood pressure, lipids, BMI, and waist circumference over time; and (3) whether the presence of metabolic syndrome components at baseline examination is associated with a longitudinal decrease in HRR. The last two aims were designed to determine the temporal relationship between HRR and the metabolic syndrome. The cross-sectional and longitudinal relationship of HRR with glucose and insulin has been previously described in CARDIA. \(^5\)
Methods

Study design

CARDIA is a longitudinal study designed to investigate the origins of cardiovascular disease in young adulthood. Detailed descriptions of study design, methods, and sample size have been previously reported. Beginning in 1985, a cohort of 5115 healthy African-American and Caucasian individuals [African-American (52%) and women (54.4%)] aged 18–30 were recruited from: Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA. Five follow-up examinations were conducted at years 2, 5, 7, 10, and 15. Of the original cohort, 3672 (72%) were examined at year 15. Reasons for not returning included inability to contact participant (n = 1029), participant refusal (n = 292), or death (n = 122), the majority of which have been non-cardiovascular-related.

Data collection

All the following measurements were collected by certified technicians according to standardized protocols at each examination. Information on demographics, physical activity, smoking, and alcohol intake were collected by interview using validated questionnaires. After a 5 min rest, seated blood pressure was measured three times with the average of the last two measurements used in analyses. Height and weight were measured with participants in light examination cloths without shoes. Waist circumference was measured using the average of two measurements taken to the nearest 0.5 cm mid-way between the iliac crest and the bottom of the ribcage while standing. Circulating glucose and lipids were collected and processed at central laboratories. Because of a laboratory drift, lipid data at year 2 were systematically elevated, and BMI (except when BMI or waist circumference were the outcome variables).

Metabolic syndrome components were defined according to National Cholesterol Education Program III guidelines, except for the cut-point for impaired fasting glucose which has been recently lowered by several organizations including the American Diabetes Association. Cut-points used were systolic or diastolic blood pressure of ≥130 or ≥85 mmHg, triglycerides ≥150 mg/dL, HDL-C <50 mg/dL (women) or <40 mg/dL (men), waist circumference ≥88 cm (women) or ≥102 cm (men), and impaired fasting glucose ≥100 mg/dL.

Exercise testing

Symptom-limited maximal graded exercise treadmill tests (GXTs) were administered according to Balke protocol at baseline and 7-year examinations using the automated Quinton stress testing system. The test included up to nine 2 min stages of increasing difficulty with participants encouraged to exercise to exhaustion, followed by a 2 min recovery period at a speed of 3.2 km/h at 0% grade. The Quinton monitoring software continuously recorded HR during testing and at each minute of recovery. HRR was defined as the difference between maximum HR and HR at 2 min into the recovery period. Ineligibility for exercise testing included evidence of ischaemic heart disease, use of cardiovascular medications, systolic or diastolic pressure >160 or >100 mmHg, or fever.

Longitudinal change in HRR was calculated as the difference between HRR at year 0 and year 7. The rate of energy expenditure, reported in metabolic equivalents (METS), for the completion of each stage of the GXT was estimated, as previously described in detail. HR increase was calculated as the difference between the pre-exercise standing HR and maximum HR.

Exclusion criteria

Main exclusion criteria included use of medications that affect HR, pregnancy, missing covariates, or missing GXT data. The final sample for cross-sectional analyses included 4319 participants.

Analyses assessing longitudinal change in risk factors levels (Aim 2) additionally excluded participants who were not examined at year 2 and at least one follow-up examination afterwards leaving 3633 participants in the sample.

In addition to the main exclusion criteria, the analysis assessing change in HRR over time (year 0 to year 7) in the presence of metabolic syndrome components (measured at year 0) additionally excluded participants who did not complete the year 7 GXT. Further, due to a GXT protocol violation at one site (participants were allowed to hold handrails) resulting in artificially skewed GXT results, data from that site were considered invalid and excluded. After these exclusions the longitudinal analysis (Aim 3) included 2222 participants.

Statistical analysis

Means and proportions of baseline demographic and clinical characteristics for the total sample were stratified by sex-specific quartiles of HRR. For continuous variables, a test linear trend was performed with HRR as a continuous variable using linear regression models. The Cochran-Armitage test was used to check for linear trend in binomial proportions across the HRR categories.

For the cross-sectional analysis, multiple linear regression models were used to assess the association of HRR as a continuous variable) with baseline levels of each metabolic syndrome component and LDL-C. Confounders previously shown or expected to influence the relationship between HRR and metabolic syndrome were controlled for in the models. These included age, sex, and race (indicator for African-American), whereas the full model additionally included smoking (current vs. non-smoker), physical activity, alcohol use, and BMI (except when BMI or waist circumference were the outcome variables).

Generalized estimating equations, with an exchangeable structure specified for within-person correlations, were used to model the relationship of baseline HRR with longitudinal change in each metabolic syndrome component and LDL-C. The regression coefficient (β) for time measured the average annual change in the outcome variable. Because higher levels of the risk factor (e.g. blood pressure) at baseline could be independently associated with greater increases in the risk factor over time, the year 2 data were used as baseline (in GEE analysis only) so year 0 levels of the risk factor could be adjusted for in the full model. The full model then included age, sex, race, time-dependent (physical activity, alcohol use, smoking, and change in BMI) BMI, and baseline risk factor measure.

Next, longitudinal change in HRR from the first to the second treadmill examination (year 0 to year 7) was compared between groups with zero (reference), one, and two or more metabolic syndrome components present at baseline examination (year 0) using general linear models. To account for baseline differences in HRR, HRR at year 0 was included as a confounder in the full model. Statistical significance was assigned at P < 0.05 and all analyses were conducted using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

Demographic characteristics of the study sample are consistent with previous reports for the full cohort (Table 1). Mean [standard deviation (SD)] HRR for the baseline study sample was 43.0 (11.3) bpm. Mean HRR did not differ among those who did and did not attend the year 15 examination (42.8 vs. 42.9 bpm, respectively), and among those who completed both years 0 and 7 GXTs and those without year 7 GXT data (43.0 vs. 42.6 bpm, respectively). Participants with slower HRR were more likely to be Caucasian, non-smokers, achieve less METs on GXT, and report less physical activity.
Cross-sectional results

HRR was associated with lipid levels and blood pressure (Table 2), such that an 1 SD lower HRR (−11.3 bpm) would be associated with triglyceride, LDL-C, and systolic blood pressure levels that are higher by 4.2 mg/dL, 2.2 mg/dL, and 1 mmHg, respectively, adjusting for age, race, and sex. Waist circumference and BMI were similarly linearly associated with increases in blood pressure, lipids (or decrease in HDL-C), waist circumference, impaired fasting glucose, and low HDL-C. The relationship was such that an 1 SD faster HRR would be expected to result in a 0.51 mmHg increase in 15 years.

Conversely, the presence of baseline metabolic syndrome components was associated with a graded decrease in HRR over time (year 0 to year 7). Group differences were apparent but not statistically significant in the age, race, and sex-adjusted model (Figure 1). In the full model, additionally adjusting for year 0 levels of HRR, the baseline presence of 1 syndrome component (n = 562) was associated with a larger decrease in HRR (P < 0.05) when compared with those with 0 (n = 1500) components, whereas the presence of ≥2 syndrome components (n = 160) was associated with a larger decrease in HRR when compared with those with both 0 and 1 components (P < 0.001 and <0.05, respectively). To determine whether any single syndrome component had a greater influence on decreasing HRR over time, we repeated analyses alternatively excluding participants with higher blood pressure, triglyceride, waist circumference, impaired fasting glucose, and low HDL-C in separate models. The associations did not change.

Longitudinal results

Over the 15-year follow-up period, slower HRR was not associated with increases in blood pressure, lipids (or decrease in HDL-C), waist circumference, or BMI (Table 3). Rather, faster HRR was associated with an increase in diastolic blood pressure over time; however, the relationship

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics according to sex-specific quartiles of HRR post-symptom-limited maximal exercise test (n = 4319)</th>
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</thead>
<tbody>
<tr>
<td>Baseline characteristics</td>
<td>All participants</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>2394 (55.4)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>1925 (44.6)</td>
</tr>
<tr>
<td>HRR</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>41.0 (11.3)</td>
</tr>
<tr>
<td>Men</td>
<td>44.0 (11.2)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>24.8 (3.6)</td>
</tr>
<tr>
<td>African-American, n (%)</td>
<td>2164 (50.1)</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>1263 (29.2)</td>
</tr>
<tr>
<td>Alcohol use (mL/day)</td>
<td>11.7 (21.2)</td>
</tr>
<tr>
<td>Length of exercise (min)</td>
<td>9.8 (2.9)</td>
</tr>
<tr>
<td>Resting heart rate (bpm)</td>
<td>69.2 (10.8)</td>
</tr>
<tr>
<td>Maximum heart rate (bpm)</td>
<td>179.0 (15.7)</td>
</tr>
<tr>
<td>Increase in heart rate from resting to maximum (bpm)</td>
<td>109.7 (18.1)</td>
</tr>
<tr>
<td>Estimated METs</td>
<td>11.9 (2.8)</td>
</tr>
<tr>
<td>Total physical activity score (exercise units)</td>
<td>418.5 (298.3)</td>
</tr>
</tbody>
</table>

*Values are expressed as mean (SD) unless otherwise indicated. NA, not applicable.
In secondary analyses, the above findings were further adjusted for baseline exercise characteristics (i.e., METs and HR increase during GXT) related to HRR (Table 1), and similar findings were observed. Further, similar associations were observed when analyses were stratified by race and sex. Lastly, analyses were repeated using HRR defined at 1 min of recovery which yielded consistent although attenuated cross-sectional results but no longitudinal associations were observed.

**Discussion**

Slower HRR following GXT was associated with higher baseline levels of metabolic syndrome components (except HDL-C) and LDL-C but not with increasing levels of syndrome components (or decrease in HDL-C) or LDL-C over the 15-year follow-up period. In contrast, the presence of metabolic syndrome components at baseline examination was associated with a greater decrease in HRR over time. Although a significant relationship of faster HRR with longitudinal increase in diastolic blood pressure was observed, the relationship was small, clinically irrelevant, and not consistent with the known association of slower HRR with increased mortality.11–13

Although previous studies have reported cross-sectional associations of HRR with glucose, insulin, waist/hip ratio, HDL-C, and the triglyceride/HDL-C ratio, this study is the first to report associations with blood pressure, triglycerides, and LDL-C.1,3–5 The association of HRR with triglyceride levels but not HDL-C was unexpected given previous reported findings.1,3 Findings for LDL-C, although not part of the metabolic syndrome, are novel and therefore presented. Notably, smoking was associated with faster HRR (Table 1), which as discussed by Sidney et al.,21 could be due to smoking-related beta-receptor down-regulation resulting in blunted HR responses to exercise.

Although HRR is known to decline with age, little is known about other factors associated with longitudinal decreases in HRR.22 The key finding of this paper is that HRR decreases faster in the presence of metabolic syndrome components, with the largest decreases occurring in those with ≥2 syndrome components. Consistent with our findings, after controlling for baseline levels of heart rate variability (HRV), Schroeder et al.,24,25 observed greater decreases in HRV over time in the presence of diabetes but did not observe similar longitudinal decreases in HRV in the presence of hyperinsulinaemia, impaired fasting glucose, or hypertension. As our results suggest, the higher prevalence of other risk factors observed in diabetics, similarly not observed in those with hyperinsulinaemia, impaired fasting glucose, or hypertension in the latter studies may explain why only diabetes was associated with a longitudinal decrease in HRV.

Only one prior study has prospectively studied the relationship of slower HRR with change in risk factor levels over time, and similarly found no association between slower HRR and an increase in levels of glucose and insulin over time.5 As proposed from experimental models, the sympathetic nervous system (SNS) is thought to have the central role in the development of the metabolic syndrome, where insulin resistance causes higher sympathetic and decreased adrenal medullary activity leading to the development of metabolic syndrome components.26 Although HR decelerations following exercise are dependent on ANS-mediated responses as well as several other factors, slower HRR may not reflect higher SNS activity.6–8 Moreover, despite its ease in measurement and widespread availability of GXTs, the use of HRR alone as a single index of the ANS has been questioned.19 These complexities need to be considered when using HRR as a surrogate measure of the ANS and when comparing HRR studies.
with the other few population-based studies on the ANS where low HRV has been predictive of incident hypertension and diabetes. 23,27,28

Study limitations need consideration. In GXT studies with upright recovery protocols, HRR has been typically defined at 1 min of recovery, whereas certain findings in our study were limited to 2 min HRR. 3,11 However, the utility of 1 min HRR in our study may have been influenced by factors unique to CARDIA such as the young age of our cohort (mean age 25 years), use of the Balke protocol which has a more gradual increase in workload with longer exercise times and the fact that GXT were maximal. Further, the metabolic syndrome is defined as the presence of ≥3 syndrome components; however, due to their young age at baseline, only a few participants met ≥3 criteria, therefore only the effect of ≥2 syndrome components on HRR could be assessed. Study strengths include the availability of repeat measurements of metabolic syndrome components and HRR as well as the extended length of follow-up.

In conclusion, our findings suggest that decreased HRR occurs after, but not before, the presence of the metabolic syndrome. These findings, along with those previously reported by Carnethon et al., on glucose and insulin for the first time provide prospective insights on the temporal relationship of the metabolic syndrome and HRR. Given slow HRR is predictive of increased mortality and cardiovascular events, 11–13 faster declining HRR in the presence of metabolic syndrome components is one possible mechanism by which the metabolic syndrome is associated with increased cardiovascular disease morbidity and mortality. 29

Acknowledgements

M.A.K. was supported by a National Research Service Award, NIH/ NHLBI post-doctoral training fellowship (T32 HL069771). M.R.C. was supported in part by a career development award from the NHLBI/NIH (5 KO1 HL73249-03). CARDIA was supported by grants and contracts from the NHLBI (N01-HC-48047, N01-HC-48048, N01-HC-48049, N01-HC-48050, N01-HC-95095).

Conflict of interest: all authors have no conflict of interests.

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