Attenuated Heart Rate Recovery After Exercise Testing and Risk of Incident Hypertension in Men

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BACKGROUND
Although attenuated heart rate recovery (HRR) and reduced heart rate (HR) reserve to maximal exercise testing are associated with adverse cardiovascular outcomes, their relation to incident hypertension in healthy normotensive populations is unclear. We examined the hypothesis that both attenuated HRR and reduced HR reserve to exercise testing are associated with incident hypertension in men.

METHODS
A total of 1,855 participants were selected comprising of healthy, initially normotensive men who underwent peak or symptom-limited treadmill testing at baseline. HRR was calculated as the difference between peak HR during exercise testing and the HR at 2 minutes after exercise cessation. HR reserve was calculated as the percentage of HR reserve (peak HR − resting HR)/(220 − age − resting HR) × 100.

RESULTS
During an average 4-year follow-up, 179 (9.6%) men developed hypertension. Incident hypertension was associated with HRR quartiles (Q1 (<42 (bpm)) 12.5%, Q2 (43–49 bpm) 8.5%, Q3 (50–56 bpm) 9.3%, and Q4 (>57 bpm) 8.3%; $P = 0.05$ for trend). The relative risk (RR) of the incident hypertension in the slowest HRR quartile vs. the fastest HRR quartile was 1.78 (95% confidence interval (CI): 1.14–2.78) after adjustment for confounders. Every 1 bpm increment in HRR was associated with a 2% (RR 0.98, 95% CI: 0.97–0.99) lower risk of incident hypertension after adjusting for potential confounders. In contrast, reduced HR reserve did not predict the risk of incident hypertension.

CONCLUSIONS
Slow HRR after exercise testing is independently associated with the development of hypertension in healthy normotensive men.

Keywords: autonomic function; blood pressure; exercise testing; heart rate recovery; heart rate reserve; hypertension.

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Although sympathetic hyperactivity increases blood pressure and predicts future hypertension,[1] few data are available regarding the longitudinal relation between parasympathetic modulation, measured via heart rate (HR) variability[2,3] or baroreflex sensitivity,[4] and incident hypertension. Some cross-sectional studies have shown that slow heart rate recovery (HRR) after exercise testing is associated with documented prehypertension and hypertension[5–7]; however, less is known about the longitudinal association between slow HRR and incident hypertension in healthy normotensive populations.[8] Because slow HRR after exercise testing as an indicator of impaired parasympathetic reactivation is an emerging prognostic index which is associated with adverse cardiovascular outcomes,[9,10] we hypothesized that slow HRR after exercise testing is associated with an increased risk of incident hypertension, independent of other risk factors. Additionally, we examined whether reduced HR reserve during exercise testing, another indicator of autonomic imbalance,[11] is related to incident hypertension.

METHODS

Participants

We initially recruited 5,616 men who participated in 2 general health examinations during 1998–2009 at Samsung Medical Center, Seoul, South Korea. Among these participants, 1,996 men who had either hypertension, cardiovascular disease or type 2 diabetes at baseline examination were excluded. An additional 1,765 men whose blood chemistry

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markers and/or HR 2 minutes following the cessation of peak or symptom-limited exercise testing were not measured at baseline were excluded. Following these exclusions, 1,855 participants (mean age 47 years; range 20–76 years) who were free of hypertension, cardiovascular disease, and type 2 diabetes, who underwent peak or symptom-limited exercise testing, and whose blood markers were measured at baseline were included in subsequent analyses. Written informed consent was obtained from all participants before the health screening program, and study methodology was approved by the medical center institutional review.

Procedures

Blood samples were collected in the morning following a 12-hour overnight fast and analyzed by the hospital clinical laboratory. Detailed methods of blood analysis have been previously described.[12] Incident hypertension was defined as systolic blood pressure (SBP)/diastolic blood pressure >140/90 mm Hg and/or diagnosed hypertension by a physician at the second examination. Blood pressure was measured during seated rest using an automated blood pressure monitor (Dinamap PRO 100, Milwaukee, WI). Resting HR was measured in the supine position using a 12-lead electrocardiogram (Hewlett-Packard ECG M1700A, Hewlett-Packard Corporation, Palo Alto, CA) following ≥5 minutes of quiet rest. Participants underwent peak or symptom-limited cardiopulmonary exercise testing using the conventional Bruce treadmill protocol. Endpoints for exercise testing included the following: (i) a rating of perceived exertion (6–20 scale) >17 (very hard) and/or a peak respiratory exchange ratio >1.15, (ii) achievement of >90% of age-predicted maximal HR, (iii) patient request because of volitional fatigue, (iv) attainment of an SBP >250 mm Hg, (v) increasing chest discomfort, (vi) threatening arrhythmias, or (vii) >1 mm of horizontal or downsloping ST segment depression. VO_{2peak} (Jaeger Oxycon Delta, Eric Jaeger, Hoechberg, Germany) was defined as the highest value of directly measured oxygen consumption, expressed as ml/kg/min, recorded during the exercise test. HR was measured during each submaximal stage, at peak exercise, and during recovery. The peak HR using 12-lead electrocardiograms (Quinton Q4500, Bothell, WA) was defined as the highest value achieved during exercise testing.

The recovery protocol included 1 minute of slow walking (1.2 mph at 0% grade) immediately after peak exercise, followed by seated resting for an additional 3 minute. HRR was calculated as the difference between peak HR attained during exercise testing and the HR at 2 minutes after cessation of exercise testing (i.e., during recovery). Abnormal HRR was defined as <42 bpm), using standard criteria as previously reported.[13] HR reserve was calculated as the percent of achieved HR reserve ((peak HR − resting HR)/(220 − age − resting HR) × 100).[14] Chronotropic incompetence was defined as <80% of HR reserve.[15]

Statistical analysis

To test for associations of HRR and HR reserve with incident hypertension, participants were divided into quartiles according to their exercise test responses. Cox proportional hazards regression with adjustment for potential confounders was used to determine the association of HRR and HR reserve quartiles, abnormal HRR, and chronotropic incompetence with incident hypertension. The cumulative curves for the incidence of hypertension according to abnormal HRR over the follow-up period used the Kaplan–Meier method and log-rank test. Statistical significance was set at $P < 0.05$. All tests for statistical significance were 2 sided. Analyses were conducted using SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0, IBM Corp., Armonk, NY).

RESULTS

Baseline characteristics of participants with and without incident hypertension during follow-up are shown in Table 1. Body mass index, resting HR, SBP/diastolic blood pressure, fibrinogen, uric acid, peak SBP/diastolic blood pressure, and follow-up years were higher, whereas peak oxygen consumption was lower in participants who developed hypertension. Participants with hypertension were also more likely to demonstrate abnormal HRR than participants without hypertension (32.4% vs. 24.2%, $P < 0.015$). Baseline characteristics of participants according to HRR quartiles are shown in Table 2. Participants in the lowest quartiles of HRR were older; had higher resting HR, triglycerides, glucose, uric acid, white blood cell count, and fibrinogen; and more likely to exhibit abnormal HR reserve (<80%) than participants in the highest quartiles of HRR. In addition, peak oxygen consumption, peak HR, HR reserve, and peak SBP were lower in participants within the lowest quartiles of HRR than their counterparts in the highest quartiles.

During an average 4-year follow-up, 179 (9.6%) men developed hypertension. Incident hypertension was associated with HRR quartiles (Q1 (<42 bpm) 12.5%, Q2 (43–49 bpm) 8.5%, Q3 (50–56 bpm) 9.3%, and Q4 (>57 bpm) 8.3%; $P = 0.05$ for trend). Table 3 shows that the relative risk (RR) of incident hypertension in the slowest HRR quartile vs. the fastest HRR quartile was 1.78 (95% confidence interval (CI): 1.14–2.78) after adjustment for age, body mass index, SBP, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, glucose, C-reactive protein, white blood cell count, fibrinogen, uric acid, peak oxygen consumption, HR reserve, peak SBP, smoking, and alcohol consumption. Every 1 bpm increment in HRR was associated with a 2% (RR 0.98, 95% CI: 0.97–0.99) lower risk of incident hypertension after adjusting for potential confounders. Figure 1 shows the cumulative incidence curve for hypertension by abnormal HRR. Baseline characteristics of participants by abnormal HRR (<42 vs. >42 bpm) are shown in Supplementary Table. The risk of developing hypertension was 1.59-fold greater (95% CI: 1.14–2.23) in our multivariate adjusted model when HRR was <42 vs. >42 bpm.

In contrast, reduced HR reserve did not predict the risk of incident hypertension across the associated quartiles (Q1 (<82%) 9.8%, Q2 (83–87%) 8.1%, Q3 (88–92%) 11.4%, and

Table 1. Baseline characteristics of participants with and without incident hypertension during follow-up (n = 1,855)

Variables	Hypertension		P value
	No (n = 1,676)	Yes (n = 179)	
Age (years)	48 ± 6	48 ± 7	0.052
Follow-up (years)	4.0 ± 1.9	4.4 ± 1.5	0.002
Body mass index (kg/m^2)	24.3 ± 2.3	25.1 ± 2.2	<0.001
Smoker	20.5%	24.0%	0.066
Alcohol intake (≥3 drinks/wk)	7.1%	7.8%	0.777
Resting heart rate (bpm)	62 ± 8	63 ± 9	0.014
Systolic blood pressure (mm Hg)	116.1 ± 11.9	122.5 ± 10.7	<0.001
Diastolic blood pressure (mm Hg)	73.6 ± 8.7	78.1 ± 7.3	<0.001
Total cholesterol (mg/dl)	201.1 ± 32.4	202.9 ± 33.8	0.500
High-density lipoprotein cholesterol (mg/dl)	48.9 ± 11.0	48.6 ± 12.6	0.724
Low-density lipoprotein cholesterol (mg/dl)	130.6 ± 28.9	132.0 ± 30.4	0.521
Triglycerides (mg/dl)	140.2 ± 74.1	140.4 ± 66.7	0.968
Glucose (mg/dl)	94.3 ± 9.7	95.3 ± 10.1	0.187
C-reactive protein (mg/dl)	0.12 ± 0.25	0.15 ± 0.21	0.203
Fibrinogen (mg/dl)	275.9 ± 53.8	290.9 ± 53.6	<0.001
White blood cell count (×10^9 cells/l)	5.9 ± 1.5	5.94 ± 1.5	0.606
Uric acid (mg/dl)	5.88 ± 1.1	6.10 ± 1.2	0.014
Peak heart rate (bpm)	157.5 ± 11.9	157.2 ± 13.7	0.730
Heart rate reserve (%)	86.8 ± 9.5	86.3 ± 10.3	0.480
Peak systolic blood pressure (mm Hg)	170.2 ± 20.2	179.1 ± 19.0	<0.001
Peak diastolic blood pressure (mm Hg)	77.3 ± 9.9	82.3 ± 10.1	<0.001
Peak oxygen consumption (ml/kg/min)	35.6 ± 4.9	34.6 ± 4.8	0.017
Heart rate at 2 minutes after exercise (bpm)	108 ± 14	109 ± 15	0.369
Heart rate recovery (bpm)	50 ± 11	48 ± 10	0.095
Abnormal heart rate recovery (<42 bpm)	24.2%	32.4%	0.015

Values are expressed as mean ± SD or %.

Q4 (>93%) 9.4%; P = 0.724 for trend). The risk of incident hypertension was not significantly higher for participants in the highest quartile compared to the lowest quartile of HR reserve after adjusting for confounding variables (RR 1.12, 95% CI: 0.71–1.76, P = 0.290) (Table 4). In addition, the risk of developing hypertension was not significantly higher (RR 1.22, 95% CI: 0.82–1.82, P = 0.327) in an adjusted model when HR reserve was <80% (n = 331) vs. >80% (n = 1,524) (data not shown).

DISCUSSION

The novel finding of the present study is that an attenuated HRR to peak or symptom-limited exercise testing was significantly associated with a higher risk of developing hypertension, independent of potential confounders including peak oxygen consumption, HR reserve, and known cardiovascular risk factors in healthy normotensive men.

The potential biologic explanation for this finding is that slow HRR after peak exercise may reflect impaired parasympathetic reactivation, along with reduced sympathetic withdrawal.[9,11] Autonomic dysfunction is associated with an increased risk of incident hypertension.[1] Slow HRR is also associated with decreased endothelial function,[16] increased inflammation,[17] arterial stiffness,[18] and atherosclerosis,[12] which are all linked to increased blood pressure.[19]

Several previous studies have demonstrated that parasympathetic nervous system activity indices, such as HR variability[2,3] and baroreflex sensitivity,[4] are associated with incident hypertension over time. However, it was unclear whether slow HRR after peak or symptom-limited exercise testing predicted hypertension in normotensive men. Although few cross-sectional studies have shown that an attenuated HRR after exercise is associated with the presence of prehypertension or hypertension,[5–7] a recent prospective study from the Aerobics Center Longitudinal Study cohort found a relation between HRR at 5-minute postexercise and incident hypertension.[8] The risk of incident hypertension was reported as lower for men with a normal HRR as compared to those with a slower HRR; however, the overall model was not significant. An important distinction between this study and the

Table 2. Baseline characteristics of participants according to heart rate recovery quartiles

Variables	Heart rate recovery (bpm)				
	Q1 (<42) (*n* = 463)	Q2 (43–49) (*n* = 482)	Q3 (50–56) (*n* = 475)	Q4 (>57) (*n* = 435)	*P* value
Age (years)	49 (6)	48 (6)	47 (5)	47 (6)	<0.001
Follow-up (years)	3.6 (1.9)	4.0 (1.8)	4.2 (1.8)	4.3 (1.9)	<0.001
Body mass index (kg/m^2)	24.5 (2.4)	24.3 (2.4)	24.5 (2.2)	24.4 (2.1)	0.649
Smokers	18.8%	23.2%	22.5%	18.4%	0.256
Alcohol intake (≥3 drinks/wk)	7.6%	7.9%	6.3%	6.9%	0.550
Resting heart rate (bpm)	65 (8.9)	63 (7.8)	61 (7.5)	58 (6.3)	<0.001
Systolic blood pressure (mm Hg)	117 (12)	117 (12)	116 (12)	117 (11)	0.940
Diastolic blood pressure (mm Hg)	74 (9)	74 (8)	74 (9)	74 (9)	0.635
Total cholesterol (mg/dl)	204 (35)	200 (31)	200 (33)	201 (31)	0.155
High-density lipoprotein cholesterol (mg/dl)	48 (11)	48 (11)	49 (12)	50 (11)	0.208
Low-density lipoprotein cholesterol (mg/dl)	133 (31)	129 (28)	130 (29)	131 (28)	0.324
Triglycerides (mg/dl)	149 (82)	145 (74)	135 (69)	133 (66)	0.002
Glucose (mg/dl)	95 (10)	95 (10)	94 (10)	93 (9)	0.003
C-reactive protein (mg/dl)	0.15 (0.35)	0.11 (0.16)	0.13 (0.24)	0.12 (0.20)	0.151
Uric acid (mg/dl)	6.0 (1.1)	5.9 (1.2)	5.8 (1.1)	5.9 (1.1)	0.006
White blood cell count (×10^9 cells/l)	6.3 (1.7)	5.9 (1.5)	5.7 (1.4)	5.7 (1.3)	<0.001
Fibrinogen (mg/dl)	285 (55)	273 (52)	278 (57)	273 (52)	0.002
Peak oxygen consumption (ml/kg/min)	33.8 (4.6)	35.3 (4.7)	36.2 (4.9)	36.5 (4.6)	<0.001
Peak heart rate (bpm)	153 (15)	158 (11)	159 (10)	160 (10)	<0.001
Heart rate reserve (%)	83 (12)	87 (9)	88 (8)	89 (8)	<0.001
Heart rate reserve <80 % (%)	30.2	15.1	14.9	10.8	<0.001
Peak systolic blood pressure (mm Hg)	169 (21)	170 (19)	171 (20)	174 (20)	0.004
Peak diastolic blood pressure (mm Hg)	78 (10)	78 (10)	77 (10)	78 (10)	0.579
Heart rate at 2 minutes after exercise (bpm)	116 (15)	112 (11)	106 (11)	97 (11)	<0.001
Heart rate recovery (bpm)	37 (5)	46 (2)	53 (2)	64 (6)	<0.001

Values are expressed as mean (SD or %).

Table 3. RRs and 95% CIs of incident hypertension according to heart rate recovery quartiles

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	*P* value
Models unadjusted	2.06 (1.36–3.13)	1.18 (0.75–1.85)	1.20 (0.77–1.87)	1 (ref.)	0.002
Model 1	1.95 (1.28–2.97)	1.16 (0.74–1.82)	1.20 (0.77–1.87)	1 (ref.)	0.007
Model 2	1.95 (1.26–3.00)	1.19 (0.75–1.87)	1.22 (0.78–1.91)	1 (ref.)	0.011
Model 3	1.78 (1.14–2.78)	1.12 (0.71–1.77)	1.22 (0.78–1.90)	1 (ref.)	0.047

Model 1: adjusted for age, body mass index, and systolic blood pressure. Model 2: adjusted for model 1 plus total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, glucose, C-reactive protein, white blood cell count, fibrinogen, uric acid, smoking, and alcohol consumption. Model 3: adjusted for model 2 plus peak oxygen consumption, heart rate reserve, and peak systolic blood pressure. Abbreviations: CI, confidence interval; RR, relative risk.

present one is the different time points used to assess HRR. The Aerobics Center Longitudinal Study defined autonomic dysfunction using slow HRR at 5-minute postexercise recovery, whereas we defined autonomic dysfunction as slow HRR at 2-minute postexercise. It has been suggested that HRR at 1 or 2-minute postexercise is more reflective of both branches of the autonomic nervous system.[20] Multiple studies have also reported that HRR at 2-minute postexercise was significantly associated with the risk of cardiovascular outcomes.[9,10,15] Shetler *et al.*[10] suggested that the first 1 or 2 minutes of HRR

after treadmill exercise testing has been validated as a prognostic indicator and should be recorded. Accordingly, our findings suggest that HRR may be an important predictor of incident hypertension, and that routine interpretation of HRR following peak or symptom-limited exercise testing should be included in the interpretive findings. Importantly, the use of HRR at 2-minute postexercise may be more sensitive as a predictive tool, particularly in younger cohorts in which age-related reductions in parasympathetic tone may not be apparent.

Admittedly, slow HRR after peak exercise testing may be influenced by impaired HR reserve during exercise. HR reserve in the present study was lower in the lowest quartiles of HRR compared with the highest quartiles of HRR. Because chronotropic incompetence may be attributed, at least in part, to impaired sympathetic activity,[11] reduced HR reserve during exercise testing, another indicator of autonomic imbalance, may also be associated with the development of hypertension. However, in the present study, reduced HR reserve did not predict the risk of incident hypertension, even in the presence of chronotropic incompetence defined as the inability to achieve 80% of the calculated HR reserve. In contrast, Prasad *et al.*[8] reported that a higher HR reserve (calculated peak HR − resting HR) was associated with a lower risk of incident hypertension. These conflicting data may be attributed, at least in part, to different calculated methods for HR reserve, racial/ethnic differences, or both. Our participants were healthy Korean men, and HR reserve was defined as the percentage of achieved HR reserve, with a value <80% defined as abnormal.[14,15] Further studies are needed to clarify whether these differences affect the association between HR reserve and incident hypertension.

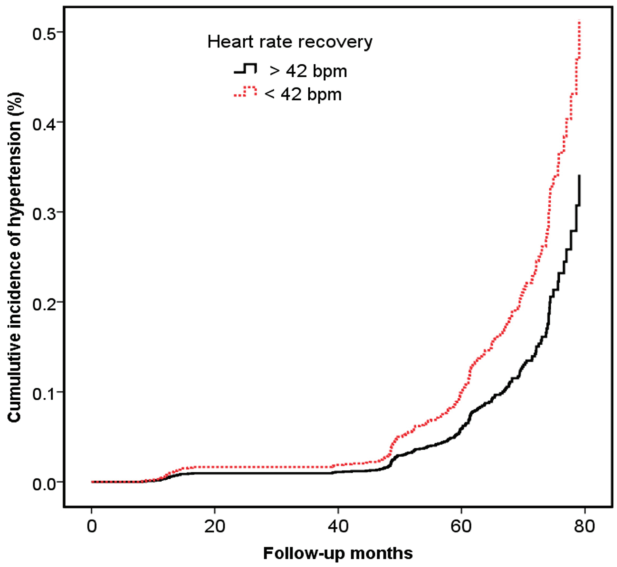

Figure 1. Cumulative curve for incident hypertension by abnormal heart rate recovery (log-rank 19.8, $P < 0.001$). Abbreviation: bpm, beats per minute.

Our results showed that delayed HRR to exercise testing was independently associated with incident hypertension after adjusting for HR reserve and other potential confounders, but that HR reserve was unrelated to this outcome. These findings further suggest that incident hypertension is associated with impaired parasympathetic reactivation as well as sympathetic derangements, as suggested in previous studies.[21] However, additional studies are needed to clarify whether HR reserve and HRR, commonly recognized indicators of autonomic dysfunction, have even greater utility as harbingers of adverse long-term cardiovascular and metabolic outcomes.

There are several limitations to our study design that require acknowledgment. Because our participants included only men, we were unable to determine whether our findings extend to women. Our database did not include information about family history of hypertension and dietary sodium intake, as well as the specific reasons for exercise test termination. Although we adjusted for multiple potential confounders as predictors of hypertension, it is possible that residual variables that were not measured may have influenced the observed difference in RRs. Finally, the percentage of achieved peak HR during exercise testing in the present study was relatively low, 91% HR_{max}; however, similar peak HR responses are commonly reported in clinical populations referred for exercise testing.

The present results demonstrated that slow HRR after exercise testing as an indicator of autonomic dysfunction was associated with incident hypertension in initially normotensive men, independent of potential confounders.

Table 4. RRs and 95% CIs of incident hypertension according to heart rate reserve quartiles

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	*P* value
Models unadjusted	1.15 (0.76–1.75)	0.90 (0.59–1.37)	1.30 (0.87–1.93)	1 (ref.)	0.326
Model 1	1.19 (0.78–1.83)	0.95 (0.62–1.45)	1.44 (0.97–2.15)	1 (ref.)	0.170
Model 2	1.26 (0.81–1.95)	0.99 (0.65–1.54)	1.43 (0.96–2.15)	1 (ref.)	0.228
Model 3	1.12 (0.71–1.76)	0.98 (0.64–1.51)	1.40 (0.94–2.10)	1 (ref.)	0.290

Model 1: adjusted for age, body mass index, and systolic blood pressure. Model 2: adjusted for model 1 plus total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, glucose, C-reactive protein, white blood cell count, fibrinogen, uric acid, smoking, and alcohol consumption. Model 3: adjusted for model 2 plus peak oxygen consumption, heart rate recovery, and peak systolic blood pressure. Abbreviations: CI, confidence interval; RR, relative risk.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *American Journal of Hypertension* (http://ajh.oxfordjournals.org).

DISCLOSURE

The authors declared no conflicts of interest.

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