Association of Blood Pressure and Heart Rate Responses to Submaximal Exercise With Incident Heart Failure: The Framingham Heart Study

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BACKGROUND: Exercise stress tests are conventionally performed to assess risk of coronary artery disease. Using the FHS (Framingham Heart Study) Offspring cohort, we related blood pressure (BP) and heart rate responses during and after submaximal exercise to the incidence of heart failure (HF).

METHODS AND RESULTS: We evaluated Framingham Offspring Study participants (n=2066; mean age, 58 years; 53% women) who completed 2 stages of an exercise test (Bruce protocol) at their seventh examination (1998–2002). We measured pulse pressure, systolic BP, diastolic BP, and heart rate responses during stage 2 exercise (2.5 mph at 12% grade). We calculated the changes in systolic BP, diastolic BP, and heart rate from stage 2 to recovery 3 minutes after exercise. We used Cox proportional hazards regression to relate each standardized exercise variable (during stage 2, and at 3 minutes of recovery) individually to HF incidence, adjusting for standard risk factors. On follow-up (median, 16.8 years), 85 participants developed new-onset HF. Higher exercise diastolic BP was associated with higher HF with reduced ejection fraction (ejection fraction <50%) risk (hazard ratio [HR] per SD increment, 1.26; 95% CI, 1.01–1.59). Lower stage 2 pulse pressure and rapid postexercise recovery of heart rate and systolic BP were associated with higher HF with reduced ejection fraction risk (HR per SD increment, 0.73 [95% CI, 0.57–0.94]; 0.52 [95% CI, 0.35–0.76]; and 0.63 [95% CI, 0.47–0.84], respectively). BP and heart rate responses to submaximal exercise were not associated with risk of HF with preserved ejection fraction (ejection fraction ≥50%).

CONCLUSIONS: Accentuated diastolic BP during exercise with slower systolic BP and heart rate recovery after exercise are markers of HF with reduced ejection fraction risk.

Key Words: exercise ■ heart failure ■ hemodynamics

Heart failure (HF) is an important global health issue affecting >23 million adults worldwide, and its prevalence continues to increase with aging of the global population.1,2 Despite our understanding of the HF syndrome and advances in its management, outcomes for patients with HF remain poor, and it continues to be a major cause of morbidity and mortality. Given the burden of HF, it is critical to identify high-risk individuals to treat them more aggressively to prevent the development of HF.

In this context, blood pressure (BP) and heart rate responses to exercise are potential biomarkers that may be related to HF risk. As the oxygen demand of working skeletal muscles increases during exercise, systemic neurohormonal activation results in an increase in cardiac output, resulting in a corresponding increase in systemic BP. Exaggerated BP and heart rate responses to submaximal exercise are harbingers of future cardiovascular disease (CVD), including HF, stroke, and all-cause mortality.3–8 Elevated exercise BP
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during submaximal exercise is also associated with the development of hypertension and subclinical disease, including left ventricular (LV) hypertrophy and impaired LV diastolic function. Delayed systolic BP (SBP) recovery after submaximal exercise is associated with risk of coronary artery disease (CAD),24,25 Delayed heart rate recovery after exercise is also a strong predictor of CAD, CVD, and all-cause mortality.26–28

To our knowledge, data are limited on the relations of BP and heart rate responses to submaximal exercise in ambulatory community-dwelling individuals and the risk of HF on follow-up. Accordingly, we investigated the associations of BP and heart rate responses to submaximal exercise with incident HF in the FHS (Framingham Heart Study). We hypothesized that an exaggerated BP response with slower BP and heart rate recoveries after submaximal exercise will be associated with a higher risk of HF.

Methods
The data that support the observations reported in the present article are available from the corresponding author on request.

Study Sample
The FHS is a longitudinal, epidemiological study of CVD that was established in 1948. Study participants attended examination cycles every 4 to 6 years, which included a medical history and physical examination, among other tests, to monitor for outcomes of interest. Children of the original FHS cohort and their spouses were enrolled in the Framingham Offspring Study starting in 1971. Participants in the Framingham Offspring Study were eligible for this investigation. All FHS participants provided written informed consent, and the Boston University Medical Center Institutional Review Board approved this study (application identifier 2676).

For the present investigation, Framingham Offspring Study participants who completed 2 stages of an exercise stress test (Bruce protocol) at their seventh examination cycle (1998–2002) were included. Among 3322 participants who attended the visit, 884 were excluded from participating in the walk test on the basis of protocol guidelines for the following reasons: prevalent CVD (n=184), had prior coronary artery bypass grafting surgery (n=55), percutaneous coronary intervention (n=39), underwent permanent pacemaker implantation (n=11), had arrhythmias at baseline (n=15), angina (n=91), orthopedic conditions (n=152), refused (n=123), or other reasons not specified (n=214); and 287 participants had their walk test terminated early because of dyspnea (n=131), the development of chest pain (n=3), arrhythmias (n=8), fatigue or lightheadedness (n=46), leg discomfort or claudication (n=33), significant hypertension (n=15), decrease in BP or ST-segment changes (n=6), or other reasons (n=45). For our investigation, we further excluded those with prevalent HF (n=1), those with no follow-up time (n=1), or those who had incomplete exercise test data (n=83). The remaining 2066 participants were the final sample size used in our analyses.

Submaximal Exercise Testing Protocol
The submaximal exercise testing protocol comprised a treadmill exercise test on a Marquette CardioSys machine. Submaximal exercise was defined as completion of stage 2 of the standard Bruce protocol (2.5 mph at 12% grade; total of 6 minutes of exercise duration). Participants with any known CAD, HF, or any physical disability precluding walking on a treadmill were excluded. Participants had a 12-lead ECG and heart rate and BP measurements at rest in supine and standing positions, during exercise, and during recovery in the supine position. BP and heart rate measurements during submaximal exercise were measured at 2 and 5 minutes, respectively, and at 3 minutes after exercise cessation.

Exposure, Outcome, and Covariates
For the present investigation, the exposures of interest were SBP, diastolic BP (DBP), and pulse pressure (PP) during stage 2 exercise; and BP and heart rate decline...
during recovery after exercise, as defined below. Each exercise variable was individually related to HF incidence, adjusting for the following covariates: age, sex, resting heart rate, current smoking, body mass index, total cholesterol/high-density lipoprotein cholesterol ratio, lipid-lowering treatment, resting SBP and DBP, use of antihypertensive medication, diabetes mellitus, fasting blood glucose, and prevalent CVD.

Participants underwent a comprehensive cardiovascular assessment, including a detailed medical history, physical examination, and laboratory workup for CVD risk factors. Height and weight were measured using a standardized protocol. SBP, DBP, and heart rate responses during stage 2 exercise (after 5 minutes of exercise) were measured by an FHS physician using a standardized protocol.29 Exercise PP was calculated by subtracting stage 2 DBP from stage 2 SBP. We also measured the change in SBP, DBP, PP, and heart rate from their measurements at stage 2 exercise to 3 minutes into recovery after cessation of exercise. Again, BP and heart rate during recovery were measured in the supine position by trained technicians using a standardized protocol.

For the present investigation, our primary outcomes of interest were incidence of HF and its subtypes, HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF), during follow-up. Nine major and 7 minor criteria were used for the diagnosis of any HF. Major criteria included paroxysmal nocturnal dyspnea or orthopnea, distended neck veins, rales, cardiomegaly, acute pulmonary edema, an S3 gallop, elevated jugular venous pressure, and a positive hepatojugular reflux. Minor criteria included ankle edema, night cough, dyspnea on exertion, hepatomegaly, pleural effusion, and tachycardia ≥120 beats per minute. A diagnosis of HF required the concomitant presence of 2 major or 1 major and 2 minor criteria. All events were adjudicated by a review panel of 3 physicians.32,33

HFrEF and HFpEF were distinguished on the basis of LV ejection fraction of <50% and ≥50%, respectively, at or in close proximity to the time of HF episode. The definition of HFrEF is a composite of cases of traditional HFrEF with ejection fraction ≤40% and HF with midrange ejection fraction with ejection fraction of 41% to 49%.34–36 Covariates used in analyses of incidence of HF subtypes were as listed above.

**Statistical Analysis**

We standardized values of stage 2 SBP, stage 2 DBP, stage 2 PP, stage 2 heart rate, and SBP recovery, DBP recovery, and heart rate recovery to a mean=0 and SD=1. Recovery of BP and heart rate variables was defined as the change from their measurement during stage 2 exercise to their values at 3 minutes into the recovery period after exercise. We used Cox proportional hazards regression to relate each standardized exercise variable (independent variable; separate model for each) to risk of HF on follow-up. We first estimated an age- and sex-adjusted model and then a multivariable-adjusted model, additionally adjusting for resting heart rate, current smoking, body mass index, total cholesterol/high-density lipoprotein cholesterol ratio, lipid treatment, resting SBP and DBP, use of antihypertensive medication, diabetes mellitus, fasting blood glucose, and prevalent CVD. Models assessing relations of SBP, DBP, and heart rate recovery also included stage 2 exercise SBP, DBP, and heart rate, respectively, as additional covariates.

We also performed secondary analyses, examining the association of each exercise variable with HFrEF and HFpEF using Cox proportional hazards regression. If the first incident HF type experienced by a participant was categorized as HFrEF, but the outcome being assessed was time to HFpEF, the participant was censored at his/her HFrEF date and not considered eligible for analyses after that time. Similarly, if the first incident HF experienced by a participant was HFpEF, in models assessing time to HFrEF as the outcome, the participant was censored at his/her date of onset of HFpEF.

The proportional hazards assumption was assessed using an interaction term of log-transformed follow-up time and the main exposures, and was met for all models. All analyses were performed using SAS version 9.4. Statistical significance was defined as a 2-sided P<0.05.

**RESULTS**

The baseline characteristics of the study sample are summarized in Table 1, and are consistent with the common prevalence of cardiovascular risk factors in midlife. Over a median follow-up of 16.8 years, we observed 85 incident HF events (35 HFpEF, 29 HFrEF, and 21 unclassifiable HF type).

**Association Between Exercise Test Variables and Incident HF**

Lower stage 2 PP was associated with a higher risk of HF, whereas higher stage 2 DBP was associated with a higher HF risk. Stage 2 SBP and heart rate were not associated with the risk of developing HF (Table 2).

We also observed an inverse association of SBP recovery and heart rate recovery after exercise with the risk of HF. DBP recovery from stage 2 exercise was not associated with the risk of developing HF (Table 2).

**Association Between Exercise Test Variables and HF Subtypes**

In our secondary analysis, we observed a higher risk of HFrEF with lower stage 2 PP and stage 2 SBP
In analyses of postexercise recovery variables, we observed that greater rapidity of changes in SBP and heart rate was associated with a lower risk of HFrEF. There was no statistically significant association between exercise BP and heart rate variables and the risk of HFpEF in our sample.

Comparison With Published Literature
Our protocol differed from other published reports because examination 7 participants completed the walk test only to stage 2 exercise. The timing of our data collection in recovery also differed from some of the published studies, leading us to using 3 minutes in recovery as our benchmark.

To our knowledge, there are no published reports in large cohort studies on the relations between exercise BP responses to submaximal stress testing and the development of HF in community-based samples. A hypertensive response to exercise has been linked to a higher risk of cardiovascular mortality, but not to HF risk specifically.37 In addition, published reports on the relations between SBP and heart rate recovery and the development of HF are lacking. Most of the studies are in patients with established HF and show an association of exercise and postexercise recovery measures, such as oxygen consumption, heart rate, and BP responses, with mortality.38–40

Potential Mechanisms
The cardiac Frank-Starling curve relates ventricular preload to stroke volume. The heart operates on a group of Frank-Starling curves rather than a single curve determined by the afterload and inotropic status of the heart. During submaximal exercise, the balance of hemodynamic forces and cardiac contractility results in an upward shift of the curve, representing increased stroke volume.41 Beyond this, at maximal exercise, stroke volume increases primarily through increased sympathetic stimulation. The Frank-Starling mechanism is, therefore, important to consider when interpreting the relations of exercise BP and heart rate responses with incident HF.

Hypertension is a premier cause of HF, including both HFrEF and HFpEF. Conduit artery dysfunction, characterized by impaired endothelium-dependent

### DISCUSSION

#### Principal Findings
In our community-based sample, we observed that higher stage 2 DBP and lower stage 2 PP during a submaximal treadmill exercise test were associated with an increased risk of developing HF over a median follow-up of 16.8 years. In analyses of variables measured during the postexercise recovery period, a rapid decline in heart rate and SBP relative to stage 2 exercise was associated with a lower risk of HF. In analyses of HF subtypes, a lower stage 2 PP and a slower SBP recovery were associated with a higher risk of HFrEF. There was no statistically significant association between exercise BP and heart rate variables and the risk of HFpEF in our sample.

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vasodilation in response to wall shear stress during exercise and central arterial stiffness, can result in exercise-induced hypertension, which, in turn, can promote LV hypertrophy and diastolic dysfunction.17,42 Exercise-induced hypertension itself imposes increased ventricular wall stress as it experiences high afterload, which can lead to HF on long-term follow-up.

Exercise DBP is dependent on peripheral arterial resistance during submaximal exercise. The inability of the systemic vasculature to dilate appropriately during exercise results in an exaggerated DBP response to exercise.43 An augmentation of systemic vascular resistance during exercise is associated with adverse cardiovascular events irrespective of resting BP measures.44

We observed that lower DBP and higher PP during submaximal exercise are associated with lower HF risk. A greater increase in DBP with exercise would seem to track with a smaller exercise PP response. Thus, a decrease in DBP with exercise, indicating adequate decrease in peripheral arterial resistance, may be associated with greater exercise PP. Therefore, greater exercise PP (representing an optimal vasodilatory peripheral response) may be inversely associated with HF risk, whereas exercise DBP maintains a direct association as an increase in DBP may be a marker of impaired peripheral vascular responses.

Slower SBP recovery at 3 minutes into recovery after exercise is associated with significant CAD on angiography, which is another premier cause of HF.45 Subclinical CAD adversely affects cardiac myocyte inotropy and may contribute to a downward shift in the Frank-Starling curve and an increased risk of ischemic HF on follow-up. Slower SBP recovery may be associated also with increased sympathetic activity and delayed parasympathetic activation after exercise.46 The relation between slower SBP recovery after submaximal exercise and development of incident HF has not been reported previously, to our knowledge. Herein, we show that slower SBP recovery at 3 minutes into recovery is associated with higher risk of overall HF and of HFrEF. It is conceivable that a rapid restoration of SBP after exercise reduces overall load on the LV after a bout of exercise.

Brisk heart rate recovery after exercise is associated with lower rates of CVD.27 Slower heart rate recovery is associated with hypertension and all-cause mortality.26,47–49 Heart rate variability during and after exercise depends, in part, on a balance of sympathetic and parasympathetic activity. In recovery, parasympathetic activity is increased through an upsurge in vagal tone, and sympathetic activity decreases, resulting in a decrease in heart rate.50,51 It is the reduction in vagal tone that appears to be linked to all-cause mortality and CVD.52,53 In our investigation, we observed that slower heart rate recovery at 3 minutes into recovery is associated with higher risk of developing any HF and of HFrEF. The exact mechanism by which this occurs needs further elucidation. It is conceivable that a slower heart rate recovery maintains a state of relative tachycardia for a longer duration after exercise, which may be a marker of reduced cardiac hemodynamic reserve.

In our analysis, stage 2 SBP exercise was not associated with the risk of HF but was associated inversely with the development of HFrEF. It is conceivable that subclinical ventricular dysfunction may be associated with a reduced ability to increase SBP with exercise. It is also possible that combining HFrEF and HFpEF cases attenuated the overall effect. The lack of association of exercise measures with HFpEF is intriguing and unexpected; it may be related to limited number of incident HFpEF events and to the causative heterogeneity of the syndrome.

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**Table 2. Association Between Exercise Test Variables and Incident HF**

| Exposure                        | Age- and Sex-Adjusted HR (95% CI)* | P Value | Multivariable-Adjusted HR (95% CI)** | P Value |
|--------------------------------|------------------------------------|---------|--------------------------------------|---------|
| Stage 2 pulse pressure          | 0.95 (0.76–1.19)                   | 0.66    | 0.73 (0.57–0.94)                     | 0.013   |
| Stage 2 systolic blood pressure | 1.15 (0.91–1.44)                   | 0.25    | 0.82 (0.62–1.07)                     | 0.15    |
| Stage 2 diastolic blood pressure| 1.30 (1.06–1.60)                   | 0.012   | 1.26 (1.01–1.59)                     | 0.043   |
| Stage 2 heart rate              | 1.14 (0.90–1.43)                   | 0.28    | 0.92 (0.69–1.23)                     | 0.59    |
| Systolic blood pressure recovery  | 0.56 (0.43–0.71)                   | <0.001  | 0.63 (0.47–0.84)                     | 0.001   |
| Diastolic blood pressure recovery| 1.24 (0.89–1.73)                   | 0.21    | 1.21 (0.82–1.76)                     | 0.34    |
| Heart rate recovery             | 0.66 (0.52–0.84)                   | 0.001   | 0.52 (0.35–0.76)                     | 0.001   |

HF indicates heart failure; and HR, hazard ratio.

*HR values are per 1-SD increase in exercise test variable.
**Adjusted for age, sex, resting heart rate, smoking status, body mass index, total cholesterol/high-density lipoprotein cholesterol ratio, resting systolic blood pressure, resting diastolic blood pressure, antihypertensive medication, lipid-lowering medication, diabetes mellitus, fasting blood glucose, and prevalent cardiovascular disease.

†Additionally adjusts for stage 2 systolic blood pressure in multivariable-adjusted model.
‡Additionally adjusts for stage 2 diastolic blood pressure in multivariable-adjusted model.
§Additionally adjusts for stage 2 heart rate in multivariable-adjusted model.
Overall, the identification of higher stage 2 SBP and DBP, lower stage 2 PP, and slower SBP and heart rate recovery after exercise may offer a way to identify high-risk individuals who could be targeted more aggressively with management of their vascular risk factor profile to prevent the development of HF.

**Strengths and Weaknesses**

The strength of our investigation lies in its large, well-characterized community sample. Data acquisition in FHS is standardized and undergoes rigorous quality control.

The main limitations of our investigation are that our sample is composed predominantly of middle-aged White men and women of European ancestry; therefore, our results may not be generalizable to other racial and age groups. In addition, submaximal exercise can be substantially different between study participants on the basis of their fitness level. With the absence of an objective measure of cardiovascular fitness, such as cardiopulmonary testing, it was not possible to match participants based on cardiovascular fitness to their ideal relative level of submaximal exercise. Given the varying relative intensities of exercise, interpretation of recovery is also challenging. Finally, there is a relatively low number of incident HF cases in this study sample, which may have led to not detecting associations.

**CONCLUSIONS**

Higher stage 2 DBP and lower stage 2 PP were associated with higher HF risk, whereas faster SBP and heart rate recovery after exercise test are inversely related with HF risk. These observations suggest that hemodynamic responses during and following moderate exercise...
(using a conventional inexpensive test used worldwide to assess risk of obstructive CAD) may be a marker of future HF risk, and may offer a way to risk stratify individuals to possibly prevent the development of HF.
