

Exercise Physiology

Heart Rate Response to Exercise Stress Testing in Asymptomatic Women

The St. James Women Take Heart Project

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Background—The definition of a normal heart rate (HR) response to exercise stress testing in women is poorly understood, given that most studies describing a normative response were predominately based on male data. Measures of an attenuated HR response (chronotropic incompetence) and age-predicted HR have not been validated in asymptomatic women. We investigated the association between HR response to exercise testing and age with prognosis in 5437 asymptomatic women.

Methods and Results—Participants underwent a symptom-limited maximal stress test in 1992. HR reserve (change in HR from rest to peak), chronotropic index, and age-predicted peak HR were calculated. Deaths were identified to December 31, 2008. Mean age at baseline was 52 ± 11 years, with 549 deaths (10%) over 15.9 ± 2.2 years. Mean peak HR was inversely associated with age; mean peak $HR = 206 - 0.88(\text{age})$. After adjusting for exercise capacity and traditional cardiac risk factors, risk of death was reduced by 3% for every 1-beat-per-minute increase in peak HR, and by 2% for every 1-beat-per-minute increase in HR reserve ($P < 0.001$). Inability to achieve 85% age-predicted HR was not an independent predictor of mortality, but being ≥ 1 SD below the mean predicted HR or a chronotropic index < 0.80 based on the prediction model established by this cohort were independent predictors of mortality ($P < 0.001$ and $P = 0.023$, respectively).

Conclusions—Chronotropic incompetence is associated with an increased risk of death in asymptomatic women; however, the traditional male-based calculation overestimates the maximum HR for age in women. Sex-specific parameters of physiological HR response to exercise should be incorporated into clinical practice. (*Circulation*. 2010;122:130-137.)

Key Words: heart rate ■ mortality ■ exercise ■ exercise test ■ women

The definition of a normal response to exercise stress testing in women is poorly understood, given that most studies describing normative response were predominantly based on male data.¹⁻⁴ In particular, the normal heart rate (HR) response to exercise in women has not been well described. Previous studies in asymptomatic men and referral populations of both men and women have demonstrated that an attenuated HR response to exercise stress testing is an independent predictor of mortality and coronary disease.⁵⁻¹⁰ An attenuated HR response to exercise is defined as chronotropic incompetence.^{5,11}

Clinical Perspective on p 137

The normal chronotropic response to exercise is based on the physiological requirement of the body to increase its cardiac output. This requires an augmentation of both the HR and the stroke volume. However, after the HR increases

above 110 to 120 beats per minute, the stroke volume ceases to increase and the HR alone contributes to the increase in cardiac output.¹² The peak HR achieved with maximal stress testing is influenced by age and sex, although the actual predicted HR for age in women remains relatively poorly defined.^{3,5,13,14}

The purpose of this study was to describe the chronotropic response to maximal exercise stress testing in a large cohort of asymptomatic, low-risk women, with the aim at characterizing a “normal” response. In addition, a variety of chronotropic measures were examined for their prognostic ability in terms of predicting both all-cause mortality and cardiac mortality.

Methods

This study was approved by the St. James Hospital and Health Centers Institutional Review Board. All authors contributed to the

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content of the manuscript, had full access to all study data, and vouch for the completeness and accuracy of the data. Data analysis was performed completely by Dr Gulati, and in part by Dr Thisted.

Participants

The participants of this study come from the St. James Women Take Heart Project, which has been described previously.^{15,16} Briefly, in 1992 a call for female volunteers from the Chicago metropolitan area resulted in a cohort of 5932 asymptomatic women. Inclusion criteria were age 35 years or older, the absence of active cardiovascular disease, and the ability to walk on a treadmill at a moderate pace. Women were excluded if they were pregnant, had experienced typical anginal symptoms, or had a myocardial infarction within the previous 3 months; weighed more than 325 pounds (147 kg); or had blood pressures of $\geq 170/110$ mm Hg before initiating the stress test.

All participants underwent a physical examination. During the recording of the resting ECG, supine blood pressures were measured by technicians using standard clinical procedures.¹⁷ Standing blood pressures were recorded before the start of the exercise treadmill.

Study-specific exclusion criteria included the following: (1) performance of the modified-Bruce Protocol ($n=109$); (2) presence of any cardiac disease, including previous myocardial infarction, documented cardiovascular disease, heart failure, or valvular heart disease ($n=91$); (3) incomplete data on cardiac risk factors ($n=11$); (4) use of β blockers ($n=284$).

Framingham Risk Score

The Framingham Risk Score has been previously described.¹⁸ The scoring for women is calculated using a point system for total cholesterol level, high-density lipoprotein (HDL), age, systolic blood pressure, diastolic blood pressure, the presence or absence of diabetes mellitus, and current smoking. The score ranges between -17 to $+25$, with higher scores indicating more cardiac risk factors.

We defined diabetes mellitus as either self-reported diabetes mellitus or nonfasting glucose level of ≥ 200 mg/dL (11.1 mmol/L).¹⁹ Total cholesterol was used for the Framingham Risk Score because the blood collected was a random sample. HDL cholesterol was assessed by the same blood analysis.

Exercise Treadmill Testing

Participants underwent a symptom-limited treadmill test according to the Bruce protocol²⁰ with exercise ECG measurements.^{21,22} Light hand rail support was allowed during the exercise treadmill test. HR and blood pressure were measured, and a 12-lead ECG was recorded before exercise, at the end of each exercise stage, at peak exercise and at 1-minute intervals during recovery, with continuous HR and rhythm monitoring throughout the duration of the stress test. The test was discontinued for limiting symptoms (angina, dyspnea, fatigue), abnormalities of rhythm or blood pressure, or marked and progressive ST-segment deviation. Target HR was not used as a predetermined end point. An abnormal ST response was defined as ≥ 1 mm ST-segment depression (horizontal or downsloping) in leads without Q waves (excluding AVR lead). ST-segment deviation was measured 0.08 seconds after the J-point, relative to the PR segment.

Exercise Capacity

The estimated exercise capacity was measured in units of metabolic equivalents (METs) and is an estimate of the maximal oxygen uptake for a given workload.^{23,24} The exercise capacity (in METs) was estimated by the speed and grade of the treadmill.²⁵

Chronotropic Response

Measures of chronotropic response included the following: (1) absolute HR achieved at the end of stage 2 of exercise stress test; (2) absolute peak HR achieved with maximal exercise stress testing; (3) HR reserve ($HR_{\text{peak}} - HR_{\text{rest}}$); (4) peak HR ≥ 1 SD below the mean HR achieved for age by cohort; (5) ability to achieve $\geq 85\%$ age-predicted HR; (6) chronotropic index (defined below).

Chronotropic Index

The measure of the chronotropic index has been described in detail elsewhere^{8,26,27} and takes into account age, physical fitness (exercise capacity), and resting HR. The chronotropic index is the ratio of the heart rate reserve (HRR) to the metabolic reserve (MR) used at peak exercise. The HRR for any stage of exercise is calculated as follows:

$$HRR = (HR_{\text{stage}} - HR_{\text{rest}}) / (100\% \text{ age-predicted peak HR} - HR_{\text{rest}})$$

where age-predicted HR = $220 - \text{age}$ by the traditional formula.

The MR for any stage of exercise is as follows:

$$MR = (MET_{\text{stage}} - 1) / (MET_{\text{peak}} - 1)$$

In healthy subjects, the chronotropic index should be ≈ 1 because there should be an association between the HR response and the metabolic work during exercise.²⁷ A low chronotropic index would imply chronotropic incompetence and has been previously set at a chronotropic index of < 0.8 in healthy adults.²⁷

Follow-Up

All-cause mortality was the primary end point. A Social Security Death Index search was performed to identify all deaths from after the baseline evaluation in 1992, up to the end of year 2008.

Statistical Analysis

Descriptive Analyses

Descriptive analyses of all variables were examined. Population characteristics between those who were chronotropically incompetent (as described below) and those who were chronotropically competent were compared using the χ^2 test for categorical variables or the Student t test for continuous variables (2-sided).

Relationship Between Peak Heart Rate and Age

The relationship between age and peak HR with exercise showed an inverse linear association. Using cubic splines, the assumption of linearity was tested and confirmed.²⁸ The mean peak HR response to exercise for age was assessed using a linear regression model between age (as the independent variable) and peak HR (as the dependent variable). This regression model was substituted for the usual peak HR prediction in measures of chronotropic index. In the past, the 100% peak age-predicted HR has been assumed to be $220 - \text{age}$.¹ We use this definition only when denoted (labeled as the "traditional estimate") and to compare with the age-predicted peak HR defined by our cohort of women using this linear regression model (labeled as the "asymptomatic women estimate"). A nomogram was constructed to estimate percent of age-predicted heart rate achieved, based on the estimate made using this cohort of asymptomatic women, as well as the traditional estimate.

Outcomes Analyses

Person-time was calculated for each woman from date of test to date of death from any cause or December 31, 2008, whichever came first. Survival analysis was performed using Cox proportional hazards regression models to determine the effect of the measures of chronotropic response on all-cause mortality. Univariate models were initially constructed. Multivariate models that included other established predictors of all-cause mortality were constructed. Tests for confounding and effect modifiers were performed. Kaplan-Meier curves were generated for survival, stratified by chronotropic response categories. The proportional hazards assumption was confirmed by visual inspection of the log ($-\log$ [survival]) curves for all Cox models.

Determination of Best Model

To determine which model was best, Akaike information criterion (AIC) values were calculated for each model.²⁹ In particular, determination of which measure of chronotropic index had the best fit was the primary question, where the new regression model for asymptomatic women could be compared with the traditional estimate. The AIC is a statistical measure of goodness of fit that

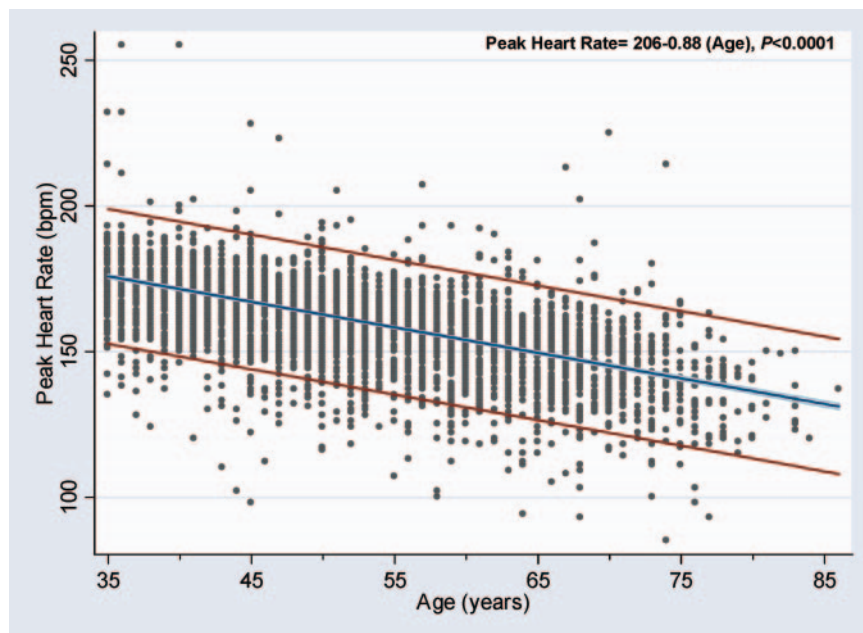


Figure 1. Graphic representation of regression equation of peak heart rate (in bpm) versus age (in years) for asymptomatic women (black line represents regression equation; black dots represent individual data points for the cohort). Inner (blue) lines represent 95% confidence limits of the mean; outer (red) lines represent 95% prediction limits (SD=11.8; $r=-0.62$; $P<0.001$).

penalizes more complex models. Smaller values of AIC imply better fit.²⁹

All analyses were performed using STATA 11.0 (College Station, Tex). Statistical significance was set at $P<0.05$ (2-sided).

Results

A total of 5437 women met the inclusion criteria for this study, with a mean follow-up time of 15.9 ± 2.2 years. There was a strong, linear relationship ($P<0.001$) between age and peak HR achieved with exercise stress testing (Figure 1), specifically:

$$\text{Peak HR} = 206 - 0.88(\text{age})$$

($N=5437$; age-adjusted SD=11.8; $r=-0.62$; $P<0.0001$) with standard errors of 0.8 and 0.015 for the constant and age coefficients, respectively. A flexible statistical model using cubic splines did not improve on the straight-line model ($P=0.64$), confirming the linear relationship between age and peak HR.

This was a symptom-limited exercise stress test and a target HR was not a predetermined end point in this study. A total of 1366 women (25%) achieved more than 100% of their age-predicted peak HR, based on the traditional estimate. Overall, 336 (7%) failed to reach at least 85% of their age-predicted HR as defined by the traditional estimate, in contrast to the 173 (3%) who failed to reach at least 85% of their age-predicted HR as defined by the asymptomatic women estimate. Similarly, 939 (17%) had a chronotropic index less than 0.8 using the traditional estimate, but only 496 (9%) had a chronotropic index less than 0.8 using the asymptomatic women estimate.

The baseline characteristics of this population have been previously described.¹⁵ Over the follow-up period, 549 (10.1%) died from any cause. The characteristics that differ by chronotropic response are listed in Table 1. Those who were chronotropically incompetent (chronotropic index less than 0.8, using the asymptomatic women estimate) were

significantly older, had a greater body mass index, higher total cholesterol, lower HDL, were more likely hypertensive, more likely to smoke, and ultimately had a higher Framingham Risk Score.

The chronotropically incompetent women had a statistically significantly higher resting systolic blood pressure than those who were chronotropically competent (Table 2). They

Table 1. Baseline Characteristics According to Chronotropic Index*

	Chronotropic Index ≥ 0.8 (n=4941)	Chronotropic Index < 0.8 (n=496)	P
Age, y	52 ± 11	55 ± 11	<0.0001
Race† (%)			
White	4222 (85)	422 (85)	0.55
Black	472 (10)	44 (9)	
Other	247 (5)	30 (6)	
Body mass index, kg/m ²	27.0 ± 5.6	29.3 ± 6.7	<0.0001
Total cholesterol, mg/dL	214.7 ± 41.0	220.7 ± 42.3	0.0021
HDL, mg/dL	52.1 ± 14.7	47.1 ± 15.2	<0.0001
Hypertension‡ (%)	2079 (42)	279 (56)	<0.0001
Diabetes mellitus§ (%)	221 (4.5)	36 (7.2)	0.005
Current smoker (%)	695 (14)	140 (28)	<0.0001
Framingham Risk Score	5.2 ± 5.9	8.0 ± 5.6	<0.0001

Values are mean $\pm$ SD unless otherwise specified. To convert HDL to mmol/L, divide by 39.

*Chronotropic index calculated using target heart rate for age, defined by this cohort where peak heart rate = $206 - 0.88(\text{age})$.

†“Other” race category includes those with no stated race.

‡Includes those with history of hypertension or resting systolic blood pressure ≥ 140 mm Hg or resting diastolic blood pressure ≥ 90 mm Hg.

§Includes those with a history of diabetes mellitus or nonfasting glucose >200 mg/dL (11.1 mmol/L).

Table 2. Exercise Testing Variables According to Chronotropic Index*

	Chronotropic Index ≥0.8 (n=4941)	Chronotropic Index <0.8 (n=496)	P
Resting HR, bpm	79±12	79±12	0.49
Resting SBP, mm Hg	128±19	132±19	<0.0001
Resting DBP, mm Hg	81±10	83±11	0.013
Stage 2 HR, bpm	145±16	125±13	<0.0001
Peak HR, bpm	162±13	135±12	<0.0001
Change in HR (peak–rest), bpm	84±15	56±13	<0.0001
Achieved ≥85% age-predicted HR (%)	4941 (100)	323 (65)	<0.0001
ST-segment depression ≥1 mm (%)	295 (6.0)	28 (5.7)	0.77
Angina (%)	30 (0.6)	10 (2.0)	<0.0001
Exercise capacity, METs	8.2±2.7	6.5±2.5	<0.0001
Peak SBP, mm Hg	165±22	164±25	0.22
Peak DBP, mm Hg	85±11	85±11	0.85

Values are mean±SD unless otherwise specified. DBP indicates diastolic blood pressure; SBP, systolic blood pressure.

*Chronotropic index calculated using target heart rate for age, defined by this cohort where peak heart rate=206–0.88(age).

also had a lower stage 2 HR, a lower peak HR, and a smaller change in HR from rest to peak exercise. All of the chronotropically competent women achieved 85% of their age-predicted HR or better (as defined using the asymptomatic women estimate), in contrast to 65% of the chronotropically incompetent women ($P<0.0001$). There was no difference in ST-segment depression between the 2 groups, but the peak exercise capacity was significantly higher in the chronotropically competent women, whereas there was more exercise-induced angina in those who were chronotropically incompetent (Table 2).

Figure 2 demonstrates the nomogram established from this cohort of women, such that the peak HR achieved with exercise stress testing can be translated into the percent of age-predicted peak HR. This is contrasted to the nomogram for the percent age-predicted peak HR based on the traditional estimate of age-predicted HR. A nomogram is a graphical representation of a mathematical equation. The nomogram is very simple to use, requiring only the woman's age and peak HR achieved (in beats per minute) on the exercise stress test. Drawing a line between the age and the peak HR will allow the determination of the percent predicted exercise capacity for age, where 100% predicted peak HR is the mean normal for any given age. Anything greater than 100% indicates better than average performance. Anything lower than 85% indicates some degree of chronotropic incompetence for age.

The univariate and multivariate hazard ratio of all-cause mortality using the different measures of chronotropic response are listed in Table 3. Each of the individual chronotropic responses was a statistically significant predictor of all-cause mortality. Resting HR was not a significant predictor of mortality. In multivariate models, after controlling for the traditional risk factors (age, diabetes, systolic blood pressure, total cholesterol, and HDL cholesterol) and exercise capacity, the chronotropic measures that remained independent predictors of all-cause mortality (in separate multivariate models) were HR at stage 2, absolute peak HR, HR reserve, being ≥1 SD below the mean peak HR for the cohort, and the chronotropic index using the formula based on the age-predicted heart rate for this cohort.

The Kaplan-Meier survival curve in Figure 2A demonstrates the difference in survival based on the chronotropic index (using the formula based on the age-predicted heart rate for this cohort). Those women with a chronotropic index <0.80 were 30% more likely to die of any cause after adjustment for traditional risk factors and exercise capacity ($P=0.023$) (Figure 3A). Women who were ≥1 SD below the

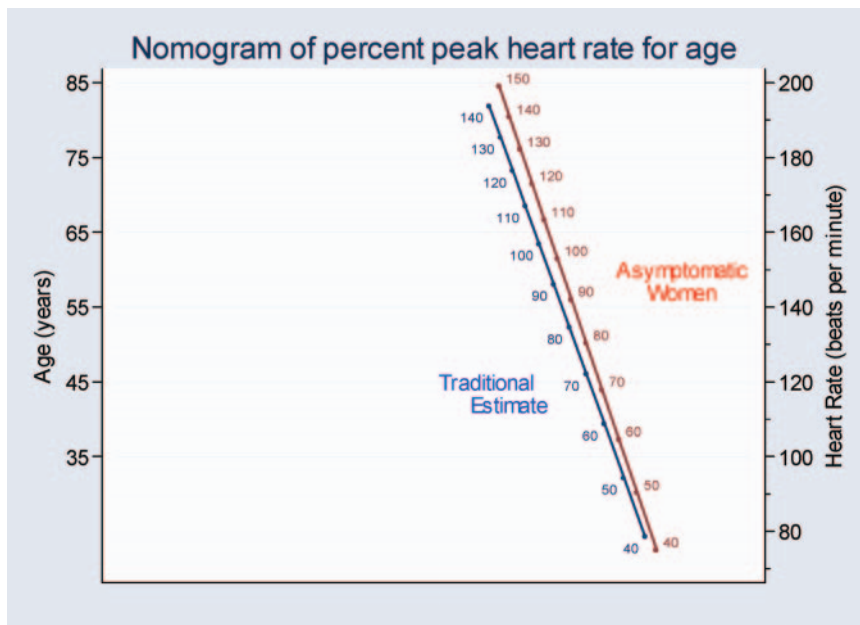


Figure 2. Nomogram of percent peak heart rate for age in asymptomatic female volunteers compared with the traditional estimate. Nomogram for asymptomatic women constructed on the basis of 100% peak heart rate for age=206–0.88(age). Nomogram for traditional estimate of peak heart rate constructed on the basis of 100% peak heart rate for age=220–(age).

Table 3. Hazard Ratio of All-Cause Mortality

Chronotropic Measures	Univariate Analysis		Multivariate Analysis	
	Hazards Ratio (95% CI)	P	Hazards Ratio (95% CI)	P
Resting heart rate (for each increase of 1 bpm)	1.00 (0.99–1.01)	0.18		
Stage 2 heart rate (for each increase of 1 bpm)	0.98 (0.98–0.99)	0.001	0.98 (0.97–0.99)	<0.001
Peak heart rate (for each increase of 1 bpm)	0.96 (0.95–0.96)	<0.001	0.97 (0.97–0.98)	<0.001
Heart rate increase to peak (for each increase of 1 bpm)	0.96 (0.95–0.97)	<0.001	0.98 (0.97–0.99)	<0.001
≥1 SD below mean peak heart rate	3.52 (2.96–4.20)	<0.001	1.84 (1.52–2.21)	<0.001
Inability to achieve ≥85% WTH* age-predicted heart rate	1.75 (1.20–2.54)	0.004	1.08 (0.74–1.58)	0.68
Inability to achieve ≥85% traditional† age-predicted heart rate	1.69 (1.28–2.22)	<0.001	1.17 (0.89–1.56)	0.24
WTH chronotropic index <0.80*	2.13 (1.70–2.67)	<0.001	1.30 (1.03–1.63)	0.023
Traditional chronotropic Index <0.80†	1.53 (1.26–1.87)	<0.001	1.11 (0.91–1.35)	0.29

Each chronotropic measure was entered into a separate multivariate model. Multivariate models controlled for traditional cardiac risk factors (age, diabetes mellitus, HDL cholesterol, total cholesterol, systolic blood pressure) and exercise capacity. WTH indicates Women Take Heart study.

*Age-predicted heart rate as defined by this cohort (WTH).

†Age-predicted heart rate as defined as 220–age (traditional).

mean peak heart rate were 1.8 times more likely to die from any cause compared with their chronotropically competent counterparts ($P<0.001$) (Figure 3B).

Using the AIC to compare the model of chronotropic index as defined by this cohort to the traditional estimate of age-predicted HR, the model using the new chronotropic index is better than the old chronotropic index model using the traditional estimate for age-predicted HR (AIC weight of the models for all-cause mortality was 9351.08 compared with 9371.47, respectively). To determine whether the difference in the AIC criterion reflects a clinically important finding, we examined the survival as a function of whether the 2 measures agreed (chronotropic incompetence by both models) or were different (chronotropic incompetence by only 1 model). As expected, the new formula identifies fewer women as being chronotropically incompetent and is a more accurate predictor of all-cause mortality. In addition, a model that included both versions of the chronotropic index showed that only the new measure of chronotropic index was statistically significant (in addition to the traditional cardiovascular risk markers and exercise capacity).

Discussion

Our study results demonstrate that chronotropic incompetence is associated with an increased risk of all-cause mortality in asymptomatic women; however, the traditional predominately male-based estimate of maximum HR for age with exercise is an overestimate for women. We describe the relationship between peak HR achieved with exercise and age in asymptomatic women and report for the first time a more accurate, sex-specific measure of chronotropic index for women, which is an independent predictor of all-cause mortality in women. Our low chronotropic index was also associated with the presence of more traditional cardiovascu-

lar risk factors and a worse performance on the exercise treadmill test.

An inverse relationship between the HR increase during exercise testing and all-cause mortality has been previously described in asymptomatic men^{8,30} and symptomatic, referral populations that included women,^{7,9} but this has not been well described in asymptomatic women. In this cohort of asymptomatic, community-dwelling women, we clearly show that stage 2 HR, peak HR, HR reserve (change in HR from rest to peak), and being ≤1 SD from the mean peak HR were also independent predictors of all-cause mortality, after controlling for traditional risk factors and exercise capacity.

Before this study, peak HR estimates and the chronotropic index were based on the assumption that the 100% age-predicted HR is 220–age for both sexes. However, the validity of this maximal HR equation has been questioned in both sexes.^{14,31} This equation was proposed by a review from Fox and Haskell,¹ which was based on 10 studies of men, where no one was older than 65 years, there was no exclusion based on β blocker use, and the studies varied in terms of inclusion of persons with established cardiovascular disease, all of which can affect maximal HR response to exercise.³² There is a small number of prior studies examining the association of age and peak HR achieved with exercise stress testing in women.^{13,14,33,34} The studies included anywhere from 44 to 357 women. All of these studies in women suggest that the traditional age-predicted maximal HR overestimates the peak HR in younger women and underestimates the predicted peak HR in older women.^{13,14,33,34} This was also suggested by a meta-analysis that looked at the age-predicted HR in women and men.³¹

The difference that we and others have noted in the age-predicted maximum HR in women is of great importance. The maximum HR is one of the most commonly used values in clinical medicine. It is used to determine the adequacy of

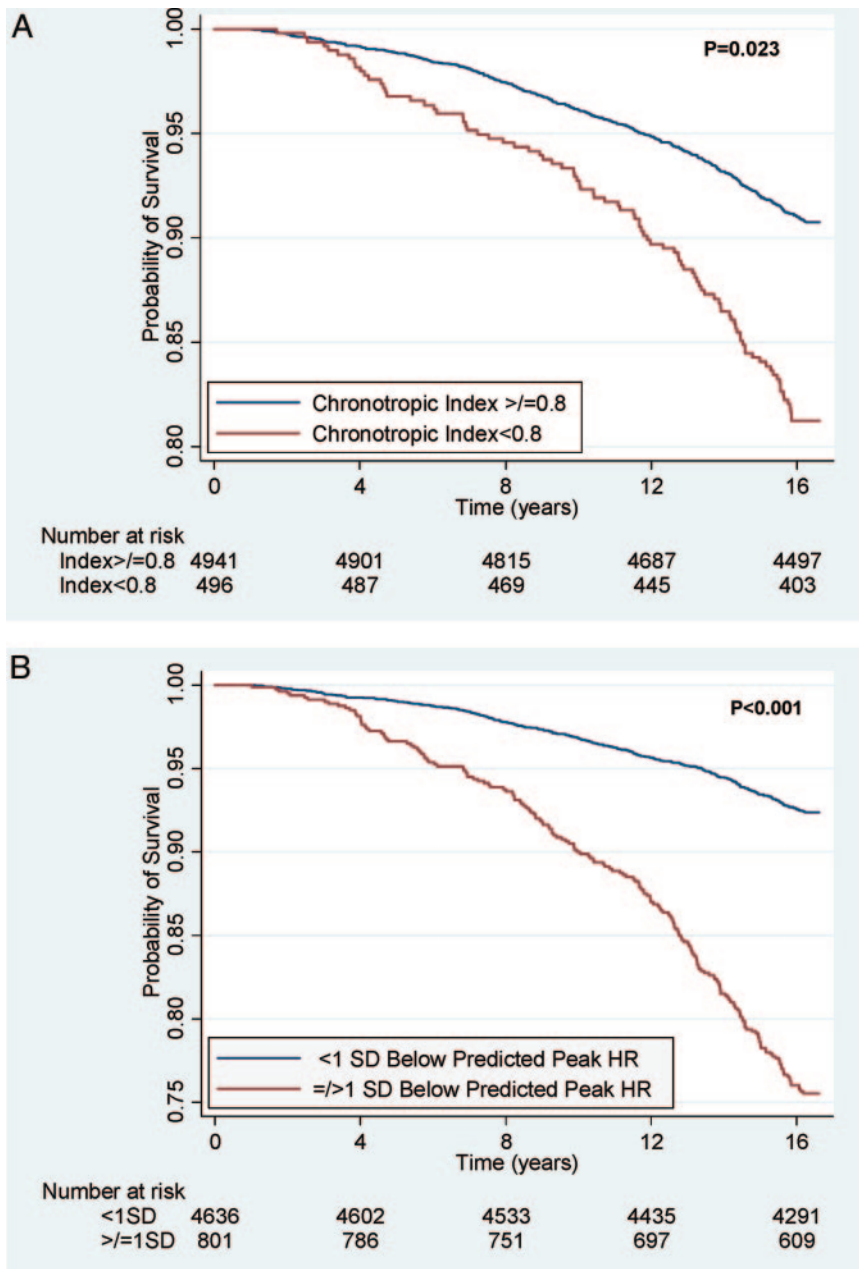


Figure 3. Kaplan-Meier survival curves by heart rate response in maximal exercise stress testing in asymptomatic women. A, Survival in asymptomatic women by chronotropic index. Chronotropic index was calculated using target heart rate for age, defined by this cohort where peak heart rate = $206 - 0.88(\text{age})$. B, Survival in asymptomatic women by predicted peak heart rate. All-cause mortality based on being ≥ 1 SD below mean peak heart rate compared with those < 1 SD from mean peak heart rate or peak HR greater than the mean peak HR.

exercise stress testing and to prescribe exercise intensity for cardiac rehabilitation and primary prevention.^{35,36} Maximal HR is often used in determination of maximal exercise capacity.^{37,38} The sex-specific difference in age-predicted maximal HR we report here likely explains the higher rates of submaximal exercise and nondiagnostic exercise stress testing results in women compared with men and therefore may contribute to the reported lower diagnostic accuracy of stress testing in women.³⁹

The use of the age-predicted maximum HR is incorporated into the calculation of the chronotropic index. Using the age-predicted maximum HR as estimated by this cohort of women, we were able to demonstrate that the chronotropic index measure was a stronger and statistically significant predictor of all-cause mortality, in contrast with the chronotropic index measure, where the traditional estimate of the age-predicted HR was used.

By definition, chronotropic incompetence means that “the heart’s response to exercise is not physiological.”⁶ The mechanism by which chronotropic incompetence may be associated with death, particularly cardiac mortality, is not entirely clear. Such an attenuated sympathetic drive is seen in persons with heart failure.^{40,41} It is possible that similar attenuation occurs in subclinical cardiovascular disease. Certainly in those with suspected coronary disease, there is an association between an impaired chronotropic response and the prevalence of significant coronary disease.^{3,42} Although it has been hypothesized that an impaired exercise HR response may be a early manifestation of cardiac ischemia,¹¹ 1 study has suggested that chronotropic incompetence may be a surrogate for underlying autonomic dysfunction, independent of myocardial ischemia.⁴³ Those with autonomic dysfunction may predispose persons to lethal arrhythmias, and therefore

increased mortality, independent of the presence or absence of coronary disease.^{44,45}

HR response to exercise may reflect a person's degree of fitness. Many prior studies, including a prior study using this cohort of women, have demonstrated an association between fitness and mortality.¹⁵ In the current results, the chronotropic index was not associated with exercise capacity ($r=0.06$), and therefore does not reflect fitness. It was also not associated with age ($r=0.02$) or resting HR ($r=0.19$). In contrast, the ability to achieve age-predicted HR was significantly associated with exercise capacity ($P<0.0001$), age ($P=0.0004$), and resting HR ($P<0.0001$). The change in HR with exercise was also correlated with exercise capacity, age, and resting HR. Therefore, the chronotropic index may be considered to be a more accurate and independent measure of chronotropic competence, as had been suggested previously, where using data from the Framingham Offspring study, asymptomatic men had very similar findings.⁸

There are potential limitations of this study. The study sample was based on a volunteer cohort. Despite the fact that the participants are not a random sample of women, estimates of our findings should be valid in similar community-dwelling populations of adult women in the United States. Another limitation is that there were only 88 women in this cohort older than 75 years, which may limit the translation of our finding in elderly women. The exercise stress test used in this study was a stepped exercise protocol. Such protocols may result in an overestimation of exercise workloads at different stages of exercise,⁴⁶ and the measurement of the chronotropic index will be limited to peak exercise. When the stress testing was performed, light use of the handrail was permitted, which is similar to most clinical settings, but may have allowed an increased exercise capacity and perhaps reduced the peak HR achieved. It is also important to note that exercise capacity was estimated, not measured directly. As a result, this would affect the calculation of the metabolic reserve and chronotropic index.

In addition to the chronotropic response to exercise, prior studies have shown that an attenuated HR recovery after exercise is an independent predictor of mortality.^{47,48} Although the HR was measured within the first minute of recovery in the majority of this cohort, the exercise recovery protocol was not standardized in this study, and it is difficult to draw any conclusion about this measure in this cohort of women.

Conclusions

We have demonstrated that sex-specific chronotropic incompetence is independently associated with an increased risk of all-cause mortality in women. Although there are many different ways to describe an impaired HR response to exercise, peak HR, HR reserve, chronotropic index <0.80 , and being ≥ 1 SD below the mean peak heart rate were all independent predictors of death. This study also demonstrates that the traditional estimate of the maximum HR for age with exercise, based on a male standard, appears to be an overestimate in women. Sex-specific parameters of physiological HR response to exercise should be incorporated into clinical practice.

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Disclosures

None.

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CLINICAL PERSPECTIVE

The definition of a normal heart rate (HR) response to exercise stress testing in women is poorly understood, given that most studies describing a normative response predominately studied men. Peak HR estimates are based on the equation of $220 - \text{age}$, which is considered the traditional estimate and is used for both sexes. The validity of this peak HR equation in women has not been described. We examined the peak HR and chronotropic response to exercise stress testing in 5437 asymptomatic women and found that the equation:

$$\text{Peak HR} = 206 - 0.88(\text{age})$$

better estimated peak HR to maximal stress testing in women, compared with the traditional estimate. In addition, incorporating this estimate for peak HR for women improved the measures of chronotropic incompetence (including inability to achieve 85% of age-predicted heart rate and a chronotropic index of <0.8) as markers of risk of all-cause mortality in women, compared with the use of the traditional estimates. Sex-specific parameters of physiological HR response to exercise should be incorporated into clinical practice. Use of this female-specific equation will improve risk prediction in women; specifically, relatively more women will achieve their age-predicted targets for greater accuracy for diagnosis and prognosis.