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Association of Chronotropic Incompetence With Echocardiographic Ischemia and Prognosis

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Objectives. **This study sought to examine the prognostic importance of chronotropic incompetence among patients referred for stress echocardiography.**

Background. **Although chronotropic incompetence has been shown to be predictive of an adverse prognosis, it is not clear if this association is independent of exercise-induced myocardial ischemia.**

Methods. **Consecutive patients (146 men and 85 women; mean age 57 years) who were not taking beta-adrenergic blocking agents and were referred for symptom-limited exercise echocardiography were followed for a mean of 41 months. Chronotropic incompetence was assessed in two ways: (1) failure to achieve 85% of the age-predicted maximum heart rate and (2) a low chronotropic index, a heart rate response measure that accounts for effects of age, resting heart rate and physical fitness.**

Results. **The primary end point, a composite of death, nonfatal myocardial infarction, unstable angina and late (>3 months after the exercise test) myocardial revascularization, occurred in 41 patients. Failure to achieve 85% of the age-predicted maximum heart rate was predictive of events (relative risk [RR] 2.47, 95% confidence interval [CI] 1.28 to 4.79, p = 0.007); similarly, a low chronotropic index was predictive (RR 2.44, 95% CI 1.31 to 4.55, p = 0.005). Even after adjusting for myocardial ischemia and other possible confounders, failure to achieve 85% of age-predicted maximum heart rate was predictive (adjusted RR 2.20, 95% CI 1.11 to 4.37, p = 0.02). A low chronotropic index also remained predictive (adjusted RR 1.85, 95% CI 0.98 to 3.47, p = 0.06).**

Conclusions. **Chronotropic incompetence is predictive of an adverse cardiovascular prognosis even after adjusting for echocardiographic myocardial ischemia.**

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Chronotropic incompetence is an attenuated heart rate response to exercise that has been shown to be independently predictive of mortality and coronary heart disease risk in healthy populations even after adjusting for age, physical fitness, standard cardiovascular risk factors and ST-segment changes with exercise (1–4). In the clinical setting, chronotropic incompetence is felt to decrease the accuracy of noninvasive imaging tests, like stress echocardiography, regarding diagnosis of significant obstructive epicardial coronary artery disease (5,6). It is not clear whether chronotropic incompetence is independently predictive of outcome among patients referred for stress testing once the presence or absence of myocardial ischemia is accounted for.

The purpose of this study was to examine the association between chronotropic incompetence and myocardial ischemia and to determine the ability of chronotropic incompetence to predict prognosis among a cohort of consecutive patients referred for exercise treadmill echocardiography in a single academic center. We also assessed the separate and combined prognostic relations of chronotropic incompetence and echocardiographic myocardial ischemia to death or major coronary artery disease events.

Methods

Study sample. Consecutive patients referred for symptom-limited exercise echocardiography at the Cleveland Clinic Foundation between September 1990 and December 1993 were considered potentially eligible for analysis if they were not taking beta-adrenergic blocking agents at the time of the exercise test. Other exclusion criteria included major valvular or congenital heart disease and referral for heart transplant or arrhythmia evaluation. All subjects gave informed consent before undergoing exercise echocardiography.

Clinical data. Before exercise testing, a structured interview and chart review yielded data on symptoms, medications, coronary risk factors, prior cardiac events and a number of cardiac and noncardiac diagnoses. Resting hypertension was

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Abbreviations and Acronyms

CI = confidence interval
HRR = heart rate reserve
LV = left ventricular
MET = metabolic equivalent
MR = metabolic reserve
NYHA = New York Heart Association
OR = odds ratio
RR = relative risk

defined as a resting systolic blood pressure ≥140 mm Hg, a resting diastolic blood pressure of ≥90 mm Hg or treatment with antihypertensive medications (7). Assessment of diabetes was based on chart review, questioning and medication use.

Exercise testing. Exercise testing procedures in our laboratory have been described in detail elsewhere (8,9). Treadmill testing was carried out according to standard protocols, usually Bruce or modified Bruce (10,11). To facilitate estimation of exercise capacity, leaning on handrails during exercise was explicitly not allowed. During each stage of exercise, data on symptoms, rhythm, heart rate, blood pressure (by indirect arm-cuff sphygmomanometry), estimated work load in metabolic equivalents (METs) and ST segments were collected and entered on-line. Estimated functional capacity in METs was estimated from standard published tables (11) based on protocol and total time completed in the final stage; a MET is a measure of oxygen consumption equal to 3.5 ml/kg/min, which represents basal, resting metabolic needs. When ST segments were interpretable, an ischemic response was considered present if there was ≥1 mm of horizontal or downsloping ST-segment depression 80 ms after the J-point or if there was ≥1 mm of additional ST-segment elevation in leads without pathologic Q waves. If a patient had more than one treadmill exercise echocardiogram performed during the study period, only the first one was considered for analysis.

Chronotropic incompetence was first assessed as failure to achieve 85% of the age-predicted heart rate. This method may be confounded by effects of age, physical fitness and resting heart rate, so chronotropic response was also assessed by calculating the ratio of heart rate reserve (HRR) used to metabolic reserve (MR) used at peak exercise; this chronotropic index has been described in detail elsewhere (1,12). Briefly, for any given stage of exercise the percent MR used is:

$$\%\text{MR used} = [(\text{METs}_{\text{stage}} - \text{METs}_{\text{rest}})/(\text{METs}_{\text{peak}} - \text{METs}_{\text{rest}})] \times 100.$$

In an analogous fashion, the percent HRR used is:

$$\%\text{HRR used} = [(\text{HR}_{\text{stage}} - \text{HR}_{\text{rest}})/(220 - \text{age} - \text{HR}_{\text{rest}})] \times 100.$$

In a group of healthy, nonhospitalized adults, the ratio of percent HRR used to percent MR used during exercise was approximately one (95% confidence interval [CI] 0.8 to 1.3). Thus, chronotropic incompetence can be defined as a percent HRR used to percent MR used ratio of <0.8; this will be referred to as a low chronotropic index. The advantage of using this approach to assess chronotropic response is that it accounts for age, functional capacity and resting heart rate; it is not merely a reflection of physical fitness or exercise time.

One problem with this method is that, except for patients undergoing sophisticated gas-exchange analyses, exercise capacity in METs is estimated and not directly measured. Because all patients in this study underwent symptom-limited testing, we chose to consider the ratio of HRR used to MR used at peak exercise, when by definition the proportion of MR used has a value of one. Thus, using this approach, the chronotropic index is based entirely on directly measured variables, namely resting heart rate, peak heart rate and age (13). Because the value of the chronotropic index is independent of stage of exercise considered, this measure takes into account effects of functional capacity as well (12).

Echocardiography. Exercise echocardiographic techniques used at the Cleveland Clinic have been described elsewhere (9). Resting and immediate postexercise images were obtained in the left lateral decubitus position using standard ultrasound imaging equipment. Images were obtained in the parasternal long- and short-axis and apical four- and two-chamber views. Data were stored on VHS videotape and also on floppy and optical disks after on-line digitization. Digital and videotape images were interpreted irrespective of image quality on the same day as the examination and were interpreted by echocardiographers who were unaware of the clinical and exercise data and of the hypothesis of this study. A standard 16-segment model of the left ventricle was used to assess for ischemia and scar. Left ventricular (LV) mass was estimated using the Penn convention (14). Echocardiographic myocardial ischemia was considered present if new or worsening wall motion abnormalities were noted in the postexercise images. Echocardiographic myocardial scar was identified by resting akinesia or dyskinesia.

Follow-up and end points. Patients were followed for a mean of 41 ± 13 months; those who underwent revascularization within the first 3 months after exercise echocardiography were considered censored. The primary end point was a composite of either death from any cause, nonfatal myocardial infarction, unstable angina or late revascularization. All end points were assessed by clinic review, telephone contact and review of records by reviewers who were unaware of exercise echocardiographic results and of the hypothesis of this study. Myocardial infarction was identified by physicians caring for the patient on the basis of clinical symptoms, electrocardiogram changes and cardiac enzyme elevations. Unstable angina was defined as angina at rest or progressive angina requiring hospitalization. Late revascularization was defined as either coronary bypass grafting or percutaneous revascularization occurring more than 3 months after the stress echocardiogram.

Statistical analyses. For analyses of baseline and exercise characteristics, subjects were divided into two groups according to ability to reach at least 85% of the age-predicted maximum heart rate on the basis of the equation 220 minus age in years. Comparisons among groups on continuous variables

were made using the Student *t* test for normally distributed variables and the Wilcoxon rank-sum test for other variables; comparisons on categorical variables were performed with the chi-square and Fisher-exact tests, as appropriate.

Chronotropic variables were related to echocardiographic myocardial ischemia and scar by calculation of unadjusted odds ratios (ORs) and CIs. To assess for possible effects of confounding while minimizing the risk for model overfitting, stepwise forward logistic regression techniques were used that required a p value of <0.05 for entry of covariates into models. Potential confounders considered included age; sex; standard cardiovascular risk factors; LV mass; LV ejection fraction; pathologic Q waves; New York Heart Association (NYHA) class; use of calcium channel blocking agents; digoxin, angiotensin-converting enzyme inhibitors and nitrates; and a history of congestive heart failure or chronic lung disease.

Chronotropic variables were related to time free of major events using log-rank chi-square statistics for unadjusted analyses, and stepwise forward Cox proportional hazards (15) analyses for multivariate analyses. Potential confounders considered included age; sex; standard cardiovascular risk factors; LV mass; echocardiographic myocardial ischemia; LV ejection fraction; pathologic Q waves; NYHA class; use of calcium blockers, digoxin, angiotensin-converting enzyme inhibitors and nitrates; and a history of congestive heart failure or chronic lung disease. Because only some patients underwent coronary angiography, angiographic findings were not considered in multivariable models. In secondary analyses subjects were divided into four groups according to exercise echocardiography results (ischemia/no ischemia) and chronotropic response (normal/abnormal). Cumulative incidence curves were calculated in each group using the Kaplan–Meier product-limit method.

All analyses were performed using version 6.12 of the SAS statistical package (SAS Institute, Cary, North Carolina).

Results

Baseline and exercise characteristics. There were 146 men and 85 women who were eligible for analyses. Of these 231 subjects, 42 (18%) failed to reach at least 85% of their age-predicted maximum heart rate, whereas 80 (35%) had a low chronotropic index—that is, they used up less than 80% of their HRR at the end of exercise.

Baseline characteristics of the study subjects according to ability to reach at least 85% of the age-predicted maximum heart rate are summarized in Table 1. Patients who failed to reach this heart rate were older; were more likely to be using calcium channel blockers, digoxin or nitrates; and were more likely to have a history of congestive heart failure or chronic lung disease; they tended to have a slightly lower ejection fraction.

Exercise characteristics according to ability to reach target heart rate are summarized in Table 2. Patients who failed to reach their target heart rate were more likely to experience angina during exercise and had a lower exercise capacity. As expected, the chronotropic index was much lower among the patients who failed to reach their target heart rate (0.53 vs. 0.94, $p < 0.0001$).

Table 1. Baseline Characteristics According to Ability to Reach at Least 85% of the Age-Predicted Maximum Heart Rate

Characteristic	Reached (n = 189)	Failed (n = 42)	p Value
Age (yrs)	56 ± 13	63 ± 10	0.0009
Female gender	67 (35%)	18 (43%)	> 0.3
Resting heart rate (beats/min)	80 ± 14	77 ± 15	> 0.3
Resting systolic blood pressure (mm Hg)	131 ± 17	132 ± 17	> 0.6
LV mass index (g/m^2)	130 ± 52	153 ± 72	0.06
LV ejection fraction (%)	56 ± 9	54 ± 11	> 0.1
Smoker	22 (12%)	9 (21%)	0.09
Hypertension	49 (26%)	17 (40%)	0.06
Electrocardiographic LV hypertrophy	83 (44%)	22 (52%)	> 0.3
Diabetes	15 (8%)	5 (12%)	> 0.4
Pathologic Q waves	31 (16%)	8 (19%)	> 0.6
Left bundle branch block	6 (3%)	3 (7%)	> 0.2
Right bundle branch block	13 (7%)	5 (12%)	> 0.3
Atrial fibrillation	7 (4%)	2 (5%)	> 0.6
Calcium channel blocker	56 (30%)	26 (62%)	< 0.001
Digoxin	23 (12%)	15 (36%)	< 0.001
Angiotensin-converting enzyme inhibitor	14 (7%)	6 (14%)	> 0.1
Lipid-lowering drug	17 (9%)	2 (5%)	> 0.3
Nitrate	19 (10%)	11 (26%)	0.005
Congestive heart failure history	8 (4%)	7 (17%)	0.003
Chronic lung disease history	5 (3%)	5 (12%)	0.002

Exercise heart rate response and wall motion abnormalities. Echocardiographic evidence of myocardial ischemia was noted in 59 patients (25%), whereas evidence of myocardial scar was noted in 49 (21%). Failure to achieve at least 85% of the age-predicted maximum heart rate was associated with echocardiographic myocardial ischemia (41% vs. 22%, unadjusted OR 2.48, 95% CI 1.22 to 5.04, $p = 0.01$) and tended to be associated with echocardiographic myocardial scar (33% vs. 19%, OR 2.03, 95% CI 0.96 to 4.32, $p = 0.06$). A low chronotropic index was similarly associated with echocardiographic myocardial ischemia (35% vs. 21%, OR 2.07, 95% CI 1.13 to 3.79, $p = 0.02$), but only tended to be associated with echocardiographic myocardial scar (27% vs. 19%, OR 1.61, 95% CI 1.61 to 3.07, $p = 0.15$).

After adjusting for possible confounders (as listed earlier), failure to achieve 85% of the age-predicted maximum heart rate tended to be associated with echocardiographic myocardial ischemia (adjusted OR 2.28, 95% CI 0.94 to 5.53, $p = 0.06$). When considered as a continuous variable, the percent of the age-predicted maximum heart rate achieved was not associated with echocardiographic myocardial ischemia. A low chronotropic index tended to be associated with echocardiographic myocardial ischemia (adjusted OR 1.93, 95% CI 0.96 to 3.90, $p = 0.07$). When considered as a continuous variable,

Table 2. Exercise Test Characteristics According to Ability to Reach at Least 85% of the Age-Predicted Maximum Heart Rate

Characteristic	Reached (n = 189)	Failed (n = 42)	p Value
Exercise capacity (METs)	8.6 ± 2.7	5.6 ± 2.2	< 0.0001
Peak heart rate (beats/min)	158 ± 18	121 ± 18	< 0.0001
Increase in heart rate (beats/min)	78 ± 21	44 ± 20	< 0.0001
Peak systolic blood pressure (mm Hg)	184 ± 26	165 ± 28	< 0.0001
Proportion of predicted heart rate achieved (%)	96 ± 8	78 ± 7	< 0.0001
Chronotropic index	0.94 ± 0.16	0.53 ± 0.11	< 0.0001
Ischemic ST-segment changes*	49/137 (36%)	12/30 (40%)	> 0.6
Angina during exercise	22 (12%)	11 (26%)	0.02

*Among subjects with interpretable ST segments.

the chronotropic index was not associated with a greater likelihood of echocardiographic myocardial ischemia. Other variables that were independently associated with echocardiographic myocardial ischemia were LV ejection fraction ($p < 0.0001$), use of calcium channel blockers ($p = 0.002$) and use of digoxin ($p = 0.04$). There were no associations between exercise heart rate parameters—considered as dichotomous or continuous variables—and echocardiographic myocardial scar after adjusting for possible confounders.

Exercise heart rate and major events. During a mean follow-up of 41 months there were 41 patients who had major events, including 7 with cardiac death, 5 with noncardiac death, 3 with nonfatal myocardial infarction, 10 with unstable angina, 5 with late coronary artery bypass surgery and 11 with late percutaneous myocardial revascularization. Patients who failed to reach 85% of their age-predicted maximum heart rate were more likely to experience major events, as noted in Figure 1 (log-rank chi-square = 8, $p = 0.005$). Similarly, patients who had a low chronotropic index (Fig. 2) were more likely to experience major events (log-rank chi-square = 9, $p = 0.004$).

In unadjusted proportional hazards models, failure to reach 85% of the age-predicted maximum heart rate was associated with risk of events (unadjusted relative risk [RR] 2.47, 95% CI 1.28 to 4.79, $p = 0.007$); similarly, the proportion of the age-predicted maximum heart rate achieved, when considered as a continuous variable, was predictive of events (for a 1-SD increase, RR 1.82, 95% CI 1.55 to 2.13, $p = 0.0002$). Analogously, a low chronotropic index was associated with risk of events (unadjusted RR 2.44, 95% CI 1.31 to 4.55, $p = 0.005$); similarly, the chronotropic index considered as a continuous variable was predictive of events (for a 1-SD increase, RR 1.65, 95% CI 1.42 to 1.92, $p = 0.001$).

Supplementary analyses were performed that considered only cardiac end points, namely, cardiac death, nonfatal myocardial infarction, unstable angina and late revascularization. There were 36 patients who had these events. Failure to reach 85% of the age-predicted heart rate was predictive of these events (RR 3.03, 95% CI 1.53 to 6.02, $p = 0.0002$), as was a low chronotropic index (RR 2.67, 95% CI 1.36 to 5.21, $p = 0.004$).

Because the exercise heart rate response was strongly associated with calcium channel blocker use (Table 1), other supplementary analyses were performed that focused on patients who were not taking these drugs. In this subset of 149 patients the proportion of the age-predicted maximum heart rate achieved, when considered as a continuous variable, was predictive of events (for a 1-SD increase, RR 1.99, 95% CI 1.46 to 2.72, $p = 0.03$), but failure to reach 85% of the predicted heart rate, considered as a dichotomous variable, was not predictive. Chronotropic index considered as a continuous variable was predictive of events (for a 1-SD increase, RR 1.88, 95% CI 1.41 to 2.49, $p = 0.03$); similarly, a low chronotropic index, considered as a dichotomous variable, was predictive of events (RR 2.85, 95% CI 1.10 to 7.38, $p = 0.03$).

Multivariate analyses. After adjusting for possible confounders (as listed earlier), failure to achieve 85% of the age-predicted maximum heart rate remained predictive of

Figure 1. Kaplan–Meier plot showing event-free survival according to ability to reach 85% of the age-predicted maximum heart rate.

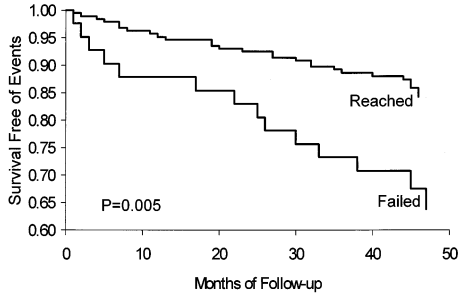
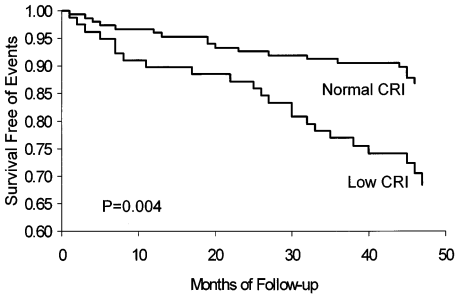


Figure 2. Kaplan–Meier plot showing event-free survival according to chronotropic index. CRI = chronotropic index.



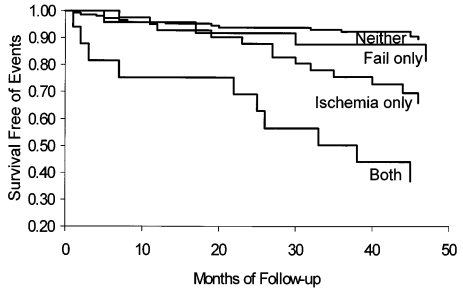


Figure 3. Kaplan–Meier plot showing event-free survival as a function of ability to reach 85% of the age-predicted maximum heart rate and the presence or absence of echocardiographic myocardial ischemia.

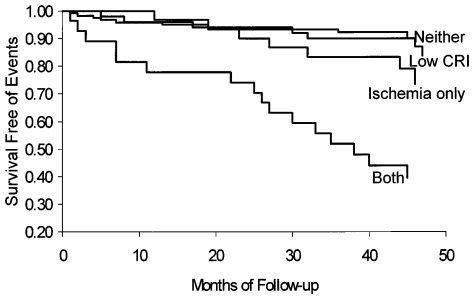


Figure 4. Kaplan–Meier plot showing event-free survival as a function of chronotropic index and the presence or absence of echocardiographic myocardial ischemia. CRI = chronotropic index.

events (adjusted RR 2.20, 95% CI 1.11 to 4.37, p = 0.02), as did a low chronotropic index (adjusted RR 1.85, 95% CI 0.98 to 3.47, p = 0.06). Similarly, the proportion of the age-predicted maximum heart rate, considered as a continuous variable, remained predictive of events even after adjusting for potential confounders (for a 1-SD increase, adjusted RR 1.65, 95% CI 1.18 to 2.19, p = 0.003). Chronotropic index considered as a continuous variable was also independently predictive of events (for a 1-SD increase, adjusted RR 1.41, 95% CI 1.04 to 1.90, p = 0.03).

Other variables that were independently predictive of events were hypertension (p = 0.002), LV ejection fraction (p = 0.02), the presence of pathologic Q waves (p = 0.03), echocardiographic myocardial ischemia (p = 0.02) and angiotensin-converting enzyme inhibitor use (p = 0.005).

Exercise heart rate, echocardiographic myocardial ischemia and events. In further analyses patients were stratified according to exercise heart rate responses and the presence or absence of echocardiographic myocardial ischemia. Patients who had normal heart rate response and no ischemia were at very low risk for events, whereas patients who had one or both abnormalities were at increased risk (Figures 3 and 4). In age-adjusted Cox regression analyses (Table 3), the combination of failure to reach 85% of the age-predicted maximum heart rate and echocardiographic myocardial ischemia was associated with a very high risk for events (adjusted RR 6.87); analogously, patients with both a low chronotropic index and echocardiographic myocardial ischemia (Table 4) were at very high risk (adjusted RR 7.05).

In separate analyses no interactions between exercise heart rate responses and myocardial ischemia were noted regarding prediction of major events.

Discussion

In a cohort of consecutive patients referred for stress echocardiography at a single center, chronotropic incompetence was predictive of subsequent death or major cardiovascular events. Both failure to achieve 85% of the age-predicted heart rate and a low chronotropic index were associated with adverse risk profiles and were weakly associated with echocardiographic myocardial ischemia; nonetheless, even after adjusting for potential confounders in stratified and multivariate analyses, chronotropic incompetence was independently predictive of risk. There were no interactions noted between exercise heart rate responses and echocardiographic myocardial ischemia; thus, their prognostic impacts were additive but not synergistic. The combination of chronotropic incompetence, especially when assessed by a low chronotropic index, and echocardiographic myocardial ischemia was not uncommon and was associated with a particularly high risk for events.

Chronotropic responses and myocardial ischemia. Exercise stress testing, whether based on electrocardiographic, nuclear or echocardiographic techniques, relies on the development of a sufficient work load to produce evidence of ischemia in the presence of significant obstructive epicardial coronary artery disease (16,17). Previous groups have focused on the decreased ability of stress imaging to accurately diagnose coronary artery disease in the presence of a submaximal heart rate response (6,18). Furthermore, it has been reported that the ability of exercise imaging to identify very low risk subsets is compromised when the heart rate response is attenuated (19). This study expands on these findings in three important respects: (1) chronotropic incompetence was associated with a greater likelihood of myocardial ischemia, although only to a mild degree; (2) despite this association, chronotropic incompetence was itself identified as an important and independent predictor of prognosis; and (3) chronotropic incompetence identified a group of patients with echocardiographic myocardial ischemia who are at particularly high risk and therefore arguably deserving of very aggressive investigation and treatment.

It has been reported that chronotropic incompetence predicts events even after considering ST-segment changes (1), which are useful though imperfect markers of myocardial ischemia (17). This study expands on these findings by taking into account effects of myocardial ischemia as assessed by an imaging technique, echocardiography, which is more accurate than electrocardiography (20). Furthermore, this study demonstrates the applicability of methods previously used in a population-based cohort, namely the Framingham Heart Study, to a clinical cohort, namely a stress echocardiography laboratory in an academic medical center.

Table 3. Age-Adjusted Cox Proportional Hazards Analyses Relating Risk of Major Events to Failure to Reach 85% of the Age-Predicted Maximum Heart Rate and Echocardiographic Myocardial Ischemia

Subset	Number	Relative Risk (95% CI)	p Value
Reached heart rate, no ischemia	147 (64%)	1.0 (—)	Reference
Failed to reach heart rate, no ischemia	25 (10%)	1.30 (0.42–4.03)	> 0.6
Reached heart rate, ischemia	42 (18%)	3.26 (1.47–7.25)	0.004
Failed to reach heart rate, no ischemia	17 (7%)	6.87 (2.91–16.18)	< 0.0001

It could be argued that our findings are merely a reflection of the association between poor exercise capacity and adverse outcome, particularly among patients whose exercise capacity is primarily limited by a heavy ischemic burden (21). The chronotropic index, however, is a measure of heart rate response that already accounts for effects of age and exercise capacity, and thus represents an isolated measure of chronotropy that provides prognostic information beyond that of functional capacity (1,12). Thus, the strong and independent association between a low chronotropic index and adverse events represents more than just the serious implications of ischemia at a low work load.

Chronotropic incompetence, coronary artery disease and prognosis. We have previously reported in a completely separate cohort of patients that chronotropic response is closely associated with the angiographic severity of coronary artery disease (22). Furthermore, in a clinical population from a different institution, the chronotropic index, measured at peak exercise as in this study, has been found to improve the diagnostic capabilities of exercise electrocardiography (13). Reports from the Framingham Heart Study have shown that in healthy community-based populations, chronotropic incompetence is a powerful and independent predictor of all-cause mortality and coronary heart disease risk, even as late as 8 years after exercise testing (1). However, no previous studies have focused on the ability of chronotropic incompetence to predict events after accounting for evidence of myocardial ischemia beyond ST-segment changes and for other potentially important echocardiographic predictors of risk, like myocardial scar or LV mass (23–25). Thus, this study strengthens the view that chronotropic incompetence should be considered as an important prognostic indicator of risk beyond other exercise and echocardiographic findings.

Mechanisms. The mechanisms by which chronotropic incompetence predicts risk are unclear. This study shows that associated myocardial ischemia alone does not entirely explain the increased risk. Chronotropic incompetence may be reflective of a modulation of autonomic tone that reflects more severe cardiovascular perturbations, as in, for example, patients with moderate to severe congestive heart failure (26,27).

Limitations. The use of a stepped protocol may lead to overestimation of exercise work loads at different stages of exercise (28); therefore, in this study measurement of the chronotropic index was limited to peak exercise. Further studies will be necessary among patients undergoing gas-exchange metabolic stress testing to confirm the association between chronotropic index, as measured in different stages of exercise, and risk. The end point assessed was a composite one that included some physician-determined end points, particularly late revascularization. Because there were only seven cardiac deaths and three nonfatal infarctions, detailed analyses on these very hard end points were not possible. We deliberately censored patients who underwent revascularization early after exercise (<3 months) to minimize bias related to physician interpretation of test results. We could have analyzed echocardiographic results in more detail, considering heart rate at ischemia and peak wall motion index, but opted not to because of problems inherent in the accuracy of their determinations (29); in contrast, looking at the presence of echocardiographic ischemia alone as a dichotomous variable has been clearly shown to accurately predict risk (9). Finally, this study does not address the issue of whether chronotropic incompetence is a potentially modifiable risk factor. It is important to recognize that we are not suggesting that chronotropic incompetence is itself a cause of increased risk, but rather is strongly associated with the occurrence of adverse events.

Conclusions. Among patients referred for exercise echocardiography for evaluation of suspected coronary disease, chronotropic incompetence is a very powerful and independent predictor of risk, even after taking into account echocardiographic evidence of myocardial ischemia. The association between chronotropic incompetence and risk for major events meets accepted criteria for a valid epidemiologic relationship.

Table 4. Age-Adjusted Cox Proportional Hazards Analyses Relating Risk of Major Events to Chronotropic Index and Echocardiographic Myocardial Ischemia

Subset	Number	Relative Risk (95% CI)	p Value
Normal chronotropic index, no ischemia	119 (52%)	1.0 (—)	Reference
Low chronotropic index, no ischemia	52 (23%)	1.15 (0.44–3.00)	> 0.6
Normal chronotropic index, ischemia	31 (14%)	2.32 (0.85–6.33)	> 0.1
Low chronotropic index, ischemia	28 (12%)	7.05 (3.06–16.27)	< 0.0001

The association was strong, with two- to threefold increases in risk. There is a temporal sequence, as demonstrated by the Kaplan–Meier plots, as well as a dose–response relationship: the worse the chronotropic response, as assessed using continuous variables, the higher the risk for events. The association persisted after adjusting for potential confounders. The results are consistent with those of previous investigations of healthy subjects and some specific patient populations. Finally, given what is known about perturbations of autonomic function and cardiovascular risk, the association is biologically plausible. Further studies will be needed to more precisely define the physiologic disorders underlying the increased risks associated with impaired chronotropic response.

All authors participated in the preparation of the manuscript. Dr. Lauer took primary responsibility for writing the manuscript and performed the data analyses. Drs. Lauer, Okin, Pashkow, and Marwick designed the study. Dr. Pashkow assembled and coordinated the exercise data base, while Drs. Mehta and Lee helped to assemble and coordinate the stress echocardiography database under the aegis of Dr. Marwick.

References

1. Lauer MS, Okin PM, Larson MG, Evans JC, Levy D. Impaired heart rate response to graded exercise. Prognostic implications of chronotropic incompetence in the Framingham Heart Study. Circulation 1996;93:1520–6.
2. Ellestad MH, Wan MK. Predictive implications of stress testing. Follow-up of 2700 subjects after maximum treadmill stress testing. Circulation 1975;51: 363–9.
3. Ellestad MH. Chronotropic incompetence. The implications of heart rate response to exercise (compensatory parasympathetic hyperactivity?). Circulation 1996;93:1485–7.
4. Chin CF, Messenger JC, Greenberg PS, Ellestad MH. Chronotropic incompetence in exercise testing. Clin Cardiol 1979;2:12–8.
5. Krivokapich J, Child JS, Gerber RS, Lem V, Moser D. Prognostic usefulness of positive or negative exercise stress echocardiography for predicting coronary events in ensuing twelve months. Am J Cardiol 1993;71:646–51.
6. Marwick TH, Nemec JJ, Pashkow FJ, Stewart WJ, Salcedo EE. Accuracy and limitations of exercise echocardiography in a routine clinical setting (see comments). J Am Coll Cardiol 1992;19:74–81.
7. The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). Arch Intern Med 1993; 153:154–83.
8. Lauer MS, Pashkow FJ, Harvey SA, Marwick TH, Thomas JD. Angiographic and prognostic implications of an exaggerated exercise systolic blood pressure response and rest systolic blood pressure in adults undergoing evaluation for suspected coronary artery disease. J Am Coll Cardiol 1995;26: 1630–6.
9. Marwick TH, Mehta R, Arheart K, Lauer MS. Use of exercise echocardiography for prognostic evaluation of patients with known or suspected coronary artery disease. J Am Coll Cardiol 1997;30:83–90.
10. Doan AE, Peterson DR, Blackmon JR, Bruce RA. Myocardial ischemia after maximal exercise in healthy men. One year follow-up of physically active and inactive men. Am J Cardiol 1966;17:9–19.
11. Fletcher GF, Balady G, Froelicher VF, Hartley LH, Haskell WL, Pollock ML. Exercise standards. A statement for healthcare professionals from the American Heart Association. Writing Group. Circulation 1995;91:580–615.
12. Wilkoff BL, Miller RE. Exercise testing for chronotropic assessment. Cardiol Clin 1992;10:705–17.
13. Okin PM, Lauer MS, Kligfield P. Chronotropic response to exercise. Improved performance of ST-segment depression criteria after adjustment for heart rate reserve. Circulation 1996;94:3226–31.
14. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. Circulation 1977;55: 613–8.
15. Cox D. Regression models and life tables (with discussion). J R Stat Soc B 1972;34:187–220.
16. Fairbarn MS, Blackie SP, McElvaney NG, Wiggs BR, Pare PD, Pardy RL. Prediction of heart rate and oxygen uptake during incremental and maximal exercise in healthy adults. Chest 1994;105:1365–9.
17. Okin PM, Kligfield P. Heart rate adjustment of ST segment depression and performance of the exercise electrocardiogram: a critical evaluation. J Am Coll Cardiol 1995;25:1726–35.
18. Beleslin BD, Ostojic M, Stepanovic J, et al. Stress echocardiography in the detection of myocardial ischemia. Head-to-head comparison of exercise, dobutamine, and dipyridamole tests. Circulation 1994;90:1168–76.
19. Sawada SG, Ryan T, Conley MJ, Corya BC, Feigenbaum H, Armstrong WF. Prognostic value of a normal exercise echocardiogram. Am Heart J 1990; 120:49–55.
20. Marwick TH, Anderson T, Williams MJ, et al. Exercise echocardiography is an accurate and cost-efficient technique for detection of coronary artery disease in women. J Am Coll Cardiol 1995;26:335–41.
21. Snader CE, Marwick TH, Pashkow FJ, Harvey SA, Thomas JD, Lauer MS. Importance of estimated functional capacity as a predictor of all-cause mortality among patients referred for exercise thallium single-photon emission computed tomography: report of 3,400 patients from a single center. J Am Coll Cardiol 1997;30:641–8.
22. Brener SJ, Pashkow FJ, Harvey SA, Marwick TH, Thomas JD, Lauer MS. Chronotropic response to exercise predicts angiographic severity in patients with suspected or stable coronary artery disease. Am J Cardiol 1995;76: 1228–32.
23. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med 1990;322:1561–6.
24. Galderisi M, Lauer MS, Levy D. Echocardiographic determinants of clinical outcome in subjects with coronary artery disease (the Framingham Heart Study). Am J Cardiol 1992;70:971–6.
25. Lauer MS, Evans JC, Levy D. Prognostic implications of subclinical left ventricular dilatation and systolic dysfunction in men free of overt cardiovascular disease (the Framingham Heart Study). Am J Cardiol 1992;70: 1180–4.
26. Colucci WS, Ribeiro JP, Rocco MB, et al. Impaired chronotropic response to exercise in patients with congestive heart failure. Role of postsynaptic beta-adrenergic desensitization. Circulation 1989;80:314–23.
27. Francis GS, Goldsmith SR, Ziesche S, Nakajima H, Cohn JN. Relative attenuation of sympathetic drive during exercise in patients with congestive heart failure. J Am Coll Cardiol 1985;5:832–9.
28. Myers J, Buchanan N, Walsh D, et al. Comparison of the ramp versus standard exercise protocols. J Am Coll Cardiol 1991;17:1334–42.
29. Hoffmann R, Lethen H, Marwick T, et al. Analysis of interinstitutional observer agreement in interpretation of dobutamine stress echocardiograms. J Am Coll Cardiol 1996;27:330–6.