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## Predicting Maximal Heart Rate in Heart Failure Patients Receiving Beta-Blockade Therapy

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### Abstract

**Purpose**—Standards for estimating maximal heart rate (HR) are important when interpreting adequacy of physiologic stress during exercise testing, assessing chronotropic response, and prescribing an exercise training regimen. The equation  $220 - \text{age}$  is used to estimate maximum HR; however, it over-estimates measured maximal HR in patients taking beta-adrenergic blockade ( $\beta$ B) therapy. This study developed and validated a practical equation to predict maximal HR in patients with heart failure (HF) taking  $\beta$ B therapy.

**Methods**—Data from symptom-limited exercise tests completed on patients with systolic HF participating in the Heart Failure and A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial and taking a  $\beta$ B agent were used to develop a simplified equation, which was validated using bootstrapping.

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#### Conflict of Interest

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**Results**—The simplified derived equation was  $[119 + 0.5(\text{resting HR}) - 0.5(\text{age}) - (0, \text{ if test was completed using a treadmill; } 5, \text{ if stationary bike})]$ . The  $R^2$  and standard error of the estimate (SEE) were 0.28 and 18 beats·min<sup>-1</sup>, respectively. Validation of this equation yielded a mean  $R^2$  and SEE of 0.28 and 18 beats·min<sup>-1</sup>, respectively. For the equation 220-age, the  $R^2$  was -2.93 and the SEE was 43 beats·min<sup>-1</sup>.

**Conclusion**—We report a valid and simple population-specific equation for estimating peak HR in patients with HF taking  $\beta$ B therapy. An equation that should be helpful when evaluating chronotropic response or assessing if a maximum effort was provided during exercise testing. We caution, however, that the magnitude of the variation (SEE=18 beats·min<sup>-1</sup>) associated with this prediction equation may make it impractical when prescribing exercise intensity.

## Keywords

Chronotropic incompetence; exercise; left ventricular systolic dysfunction; testing

## Introduction

Reference standards for maximal heart rate (HR) are important to help interpret the adequacy of physiologic stress during graded exercise testing, identify the presence of chronotropic incompetence, and prescribe an exercise training regimen when measured maximal HR is not available. Although the equation 220 – age remains the common *de facto* method for estimating maximum HR in healthy adults, its accuracy has been challenged if used in different patient populations or during different modes of exercise (18). Brawner et al. (3) demonstrated that the 220 – age equation is not valid in patients with coronary heart disease taking beta-adrenergic blockade ( $\beta$ B) therapy and yields a prediction error of  $40 \pm 19$  (mean $\pm$ sd) beats. Since  $\beta$ B therapy is routinely prescribed for the management of patients with heart failure (HF) due to left ventricular systolic dysfunction (14), determining whether or not maximum effort was put forth, as judged by peak HR achieved during exercise testing, can be difficult. However, it remains important, because such testing is often used to (a) assess chronotropic response, (b) detect the presence of inducible ischemia, or (c) prescribe exercise.

The multi-center Heart Failure and A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial was a prospective clinical trial conducted in patients with chronic HF and included a standardized cardiopulmonary exercise testing protocol. Using the data from the symptom-limited maximum exercise tests completed in the HF-ACTION trial at baseline, this report describes a practical equation to predict maximal exercise HR in patients with chronic HF taking a  $\beta$ B as part of evidence-based therapy.

## Methods

### Study Sample

The design, subject eligibility criteria, and methods of HF-ACTION have been previously described (21). Briefly, between April 2003 and February 2007, 2331 patients were enrolled from 82 participating clinical sites. Inclusion criteria included New York Heart Association Class II, III or IV HF and a left ventricular ejection fraction  $\geq 35\%$ . Clinical site personnel were encouraged to ensure that subjects were on stable guideline-based pharmacologic therapy for at least six weeks prior to randomization. The protocol was approved by the Institutional Review Board or Ethics Committee for each center and patients provided written informed consent.

For the present study we excluded subjects in HF-ACTION who had a pacemaker (n=360), were in any rhythm other than sinus (n=453), or were not on  $\beta$ B therapy (n=128). To help

control for the potentially different effects of various  $\beta$ B agents on peak HR,  $\beta$ B doses were converted to equivalent doses of carvedilol based on dosing from clinical trial data and published studies evaluating the conversion of  $\beta$ B agents (6,12,15). Specifically, the daily dosage in patients taking atenolol (n=24), metoprolol (n=54), or metoprolol XL (n=200) was divided by 2; the dose for bisoprolol (n=31) was multiplied by five.

We also excluded patients (n=149) whose baseline exercise test was stopped primarily due to a reason other than fatigue or dyspnea (i.e., angina, adverse changes in blood pressure, orthopedic/musculoskeletal complaints, or electrocardiographic evidence of ischemia or arrhythmia). To help ensure the exercise HR data used in this analysis was gathered from patients who provided a maximal effort during cardiopulmonary exercise testing, data from patients in HF-ACTION who achieved a respiratory exchange ratio (RER) < 1.06 during cardiopulmonary testing were excluded as well (n=433). Forty-one patients were excluded because of missing data (RER, exercise mode).

### Exercise Testing

After randomization into the HF-ACTION trial, subjects were scheduled to complete a symptom-limited maximum exercise test, with open circuit spirometry for analysis of expired gases. Testing was performed in accordance with American College of Cardiology and the American Heart Association guidelines (11). To assess for and minimize any re-test related familiarization effect, the first five subjects to undergo exercise testing at each participating site in HF-ACTION performed two such tests within one week at baseline (2). For those patients with two tests at baseline, this study used data from the first test. Subjects were instructed to take their medications as prescribed on the day of testing, with a specific request that they take their  $\beta$ B agent between three and 10 hours before the test.

The primary mode of testing was a treadmill; however, a stationary cycle ergometer was used for 84 patients (11%) unable to walk on the treadmill or tested at sites that routinely used this modality for exercise testing. Site testing personnel were instructed to exercise patients to an endpoint of exhaustion. They were instructed to use as a guide a Borg rating of exertion level that was >16 (scale 6 to 20) and/or an RER of >1.10, but not to use achievement of either of these two criteria as a reason to stop a test. Resting HR was measured prior to testing, after two minutes of seated rest. Maximal HR represented the highest HR achieved during the last minute of exercise.

### Statistical Analysis

Consistent with the statistical methods used previously in the HF-ACTION trial (8), a comprehensive list of 33 resting clinical and demographic variables obtained from baseline case report forms and clinical assessments were assessed as predictors of maximal HR. Multiple linear regression was used with variable selection in two stages. First, a stepwise backwards selection algorithm was used in which the variable with the highest P-value was removed, the model was then re-fit and the variable with the highest P-value in the new model was removed. This process was repeated until all remaining covariates had  $P < 0.05$ . The second stage removed, in a single step, all variables with a partial  $r^2 < 0.01$ .

A full model inclusive of the remaining parameters with the associated overall  $R^2$ , standard error of the estimate (SEE), and the P-value and partial  $r^2$  value for each parameter was rendered. Three reduced, 1- or 2-factor candidate equations were generated using the two variables that explained most of the variation in the full model. Interaction tests were included in each of these reduced three models to determine whether the relationship of predictors of maximal HR varied significantly between gender or  $\beta$ B doses. No significant

interactions were found; therefore, a single prediction equation (with an adjustment for equipment type) can be used for the entire cohort.

Six candidate prediction equations were developed: three based on the regression coefficients of the above mentioned reduced models and, using these same equations, three more as a simplified equation that allowed for easier use in the clinical setting. Simplified versions were developed by rounding the coefficients to the nearest 0.5, and then solving for an intercept such that the simplified line would go through the same predicted maximal HR as the fitted regression line at the mean values of predictors (i.e. within 0.5 beats·min<sup>-1</sup> at the mean values).

Based on both statistical and clinical considerations, one main simplified equation was selected to be validated. Bootstrapping was used for validation. Bootstrapping is superior to data splitting (i.e., creating “derivation” and “validation” cohorts) because it uses the entire sample for both derivation and validation, allowing better estimation of model performance than subsamples; further, it is not subject to the chance element of a single, possibly fortuitous split in the data. From our study sample, 200 bootstrap samples were drawn; each at random and with replacement, yielding the same size as the original sample. Thus, the process generates samples that are representative of those that would be obtained if repeated sampling were carried out on the actual population. The validation process then consisted of finding, within each bootstrap sample, the R<sup>2</sup> and SEE based on the primary equation; calculating the mean and standard deviation of these measures across all bootstrap samples; and comparing to those in the original sample. Because of its common use in exercise testing laboratories, the performance of the equation of 220-age in predicting maximal HR was also evaluated by calculating R<sup>2</sup> and SEE.

## Results

Table 1 summarizes the demographic and clinical characteristics of the 767 individuals whose baseline exercise tests were included in this analysis. The full predictive model for maximal HR containing the pre-specified candidate variables yielded an R<sup>2</sup> = 0.41 and an SEE = 17 beats·min<sup>-1</sup>. The seven candidate variables that were independent (p<0.05 and partial r<sup>2</sup> = 0.01) predictors of maximal HR in the full multivariable model are shown in Table 2 (over-all model R<sup>2</sup> = 0.36; SEE = 17 beats·min<sup>-1</sup>).

### Selection of Main Simplified Equation

Age and resting HR explained most of the variation in the full model (Table 2). The three regression prediction equations and associated R<sup>2</sup> and SEE values using these two variables are shown in Table 3. Each regression equation in this table is accompanied by a simplified equation. From the six equations in Table 3, equation number two [119 + 0.5(resting HR) – 0.5(age) – (0, if test was completed using a treadmill; 5, if test was completed using a stationary bike)] was selected as our main simplified equation, because in its simplified form it had the highest R<sup>2</sup> (0.28) and lowest SEE (18 beats·min<sup>-1</sup>).

### Validation of Main Simplified Equation

Validation of our main simplified equation using 200 bootstrap samples yielded a mean R<sup>2</sup> and SEE of 0.28 ± 0.02 (mean±SD) and 18 ± 1 beats·min<sup>-1</sup>, respectively. As a comparison, the performance of the standard 220-age formula was also evaluated in our cohort and the R<sup>2</sup> was –2.93 and the SEE was 43 beats·min<sup>-1</sup>. An R<sup>2</sup> < 0 occurs when predictions are further from the actual values than the sample mean; very poor predictions can produce an R<sup>2</sup> < –1.

## Discussion

The common equation for predicting maximal exercise HR of 220-age has been in use for decades (9,18) and when used in people free of clinically manifest disease, is usually associated with a SEE of 10–12 beats·min<sup>-1</sup> (1). In our analysis of data from exercise tests completed in patients with stable HF taking  $\beta$ B therapy, we showed that the above common equation does not accurately predict maximal HR (i.e., SEE = 43 beats·min<sup>-1</sup>). Instead, we report a simple population-specific equation to predict maximal HR during treadmill testing [ $119 \pm 0.5(\text{resting HR}) - 0.5(\text{age})$ ], one that performed well throughout a multi-step validation process. Specifically, the R<sup>2</sup> (0.28) and the SEE (18 beats·min<sup>-1</sup>) for our simplified primary equation derived from the original sample were the same as the mean R<sup>2</sup> and the SEE from our validation process using bootstrapping. It is important to point out that, despite this concordance, the absolute SEE of 18 beats·min<sup>-1</sup> is still slightly large and reflects a fair amount of individual variation; possibly due to the generally diverse nature of the cohort, inter-subject differences in disease severity, and inter-subject differences in the response of HR to therapies.

### Comparison to Other Prediction Equations

The equation we propose to predict maximal HR is specific for patients with chronic HF on  $\beta$ B therapy and its' associated SEE of 18 beats·min<sup>-1</sup> is consistent with values reported previously by others for equations in apparently healthy people (4,7,10,16,17,19,20), patients with heart disease (3,4,13) and patients with heart disease taking a  $\beta$ B (3). That said, our SEE of 18 beats·min<sup>-1</sup> represents more than 10% of our mean peak HR of 125 beats·min<sup>-1</sup> and is likely due to factors such as inter-individual differences in both disease severity and co-morbid conditions. A prospective study involving patients with more uniform HF symptoms, functional class, and associated co-morbidities would likely help yield a predictive equation that is associated with a SEE less than 18 beats·min<sup>-1</sup>, but would do so at the expense of generalizability.

Applying the prior equation from Brawner, et al. (3) that was derived from patients with heart disease taking  $\beta$ B therapy [ $164-0.7(\text{age})$ ] to our sample of patients with HF taking  $\beta$ B therapy, we observed a lower R<sup>2</sup> (0.18) and a similar SEE = 19. A reason for the higher R<sup>2</sup> (0.28) in our equation is likely its use of both age and resting HR (versus age only) in the model. It is important to point out that the inclusion of age in both equations indicates that this parameter is an important and strong predictor of maximal HR, similar to like equations advanced by others previously (20). Additionally, in our analysis resting HR was the strongest predictor (Table 2, partial R<sup>2</sup> = 0.14) of maximal HR, likely related to the effect of  $\beta$ B therapy.

We advance that our simplified, two variable population-specific equation provides a convenient and relatively good estimate of maximal HR in patients with chronic HF on  $\beta$ B therapy. Provided with both a subject's age and resting HR after 2 minutes of seated rest, an approximate maximal HR can be quickly determined (Table 4). Additionally, our subgroup analyses addressing gender or  $\beta$ B dose used during testing revealed no interaction effect, suggesting that our single prediction equation has broad generalizability. If testing is completed on a stationary cycle ergometer, the estimated maximal HR calculated using our simplified equation should be reduced by 5 beats·min<sup>-1</sup>. Although this equation was internally validated using the bootstrapping methodology, external validation using data from another cohort comprised of patients similar to those used in our study would prove helpful.

## Beta-adrenergic Blockade Therapy and Maximal Heart Rate

As previously shown by others (3) and as evidenced by our results in this study, among patients with heart failure taking a  $\beta$ B agent the commonly used 220-age equation overestimates maximal HR and is associated with SEE that can exceed 40 beats·min<sup>-1</sup>. Given the chronotropic effect of  $\beta$ B, this finding is not surprising. Although we controlled for the effect of different doses from different  $\beta$ B agents by equating all doses to carvedilol equivalents, we acknowledge that differences in disease severity may influence the degree of down-regulation in beta<sub>1</sub> receptor sensitivity to endogenous norepinephrine and, therefore, might have influenced chronotropic response (5). We did test for an interaction effect involving  $\beta$ B dose and found no interaction or main effect, indicating that no adjustment for  $\beta$ B dose was necessary.

### Importance of Maximal Effort

To help establish an equation that predicts maximum HR, we excluded those patients whose exercise test appeared to be submaximal in effort (RER <1.06), was stopped due to reasons other than fatigue or dyspnea (e.g., chest pain), had a pacemaker, or had a heart rhythm other than sinus. Evidence that maximal effort was achieved by patients in our study cohort during testing includes attainment of a median RER and a median rating of perceived exertion of 1.13 units and 17 units, respectively (Table 1). Based on this, we believe that our primary equation for predicting maximal HR [ $115 + 0.5(\text{resting HR}) - 0.5(\text{age})$ ] is generalizable to similar patients with HF on  $\beta$ B therapy seen in the clinical setting, and provides a predicted maximum HR value against which exercise HR values measured during testing in future patients can be evaluated.

### Clinical Application during Testing Performed Without Gas Exchange

When exercise testing is conducted without the simultaneous collection of gas exchange and the measurement of RER, the use of an equation to predict maximal HR to help determine if maximum exercise effort is achieved becomes particularly useful and important in patients with HF taking a  $\beta$ B. For example, when stress testing is performed simply for the purposes of either detecting the presence of inducible ischemia (i.e., stress echocardiogram) or assessing chronotropic response (22), using estimated maximal HR derived from a population-specific prediction equation such as the one we propose can help qualitatively interpret the level of effort achieved. Despite the temptation to use our simplified prediction equation to determine a target HR range for exercise training, we recommend the use of formal exercise testing when prescribing a HR-based exercise training intensity level in patients with HF. In these patients a SEE of 18 beats·min<sup>-1</sup> makes our prediction equation impractical for prescribing exercise.

### Potential Limitations

Like all retrospective analyses, there may have been variables that we did not measure or variables that we did measure but were not included as a candidate variable. However, we believe that most of the common parameters presently known to markedly affect exercise capacity or chronotropic response were accounted for in our analysis. In fact, and consistent with current treatment guidelines, a strength of this study is that all patients were taking  $\beta$ B therapy and for this analysis all doses, regardless of the specific  $\beta$ B, were adjusted to carvedilol equivalents. Another potential limitation is that some older patients and patients felt to be too ill to participate in an exercise training trial may not have been enrolled into HF-ACTION, potentially limiting the validity of our equation in such patients. Nonetheless, our cohort of patients (n=767), in sinus rhythm (no pacemaker, no atrial fibrillation), is representative and generalizable to like patients with stable chronic HF due to systolic dysfunction on evidence based therapy, with 25% greater than or equal to 66 years of age,

30% female, 41% non-Whites, a median ejection fraction of 25%, a median peak  $\text{VO}_2$  of  $15.7 \text{ mL kg}^{-1} \text{ min}^{-1}$ , and nearly 50% with an ischemic cardiomyopathy.

## Conclusion

We showed that the common equation of 220-age does not accurately estimate maximal HR in patients with HF due to systolic dysfunction taking a  $\beta\text{B}$  as part of their guideline recommended therapy. Instead, we report a valid and simple population-specific equation [ $119 + 0.5(\text{resting HR}) - 0.5(\text{age})$ ] for estimating peak heart rate in patients with HF taking  $\beta\text{B}$  therapy. This equation can help evaluate chronotropic response or assess if a maximum effort was put forth during exercise testing. We caution, however, that the magnitude of individual variation ( $\text{SEE}=18 \text{ beats min}^{-1}$ ) associated with this prediction equation may render it somewhat impractical for prescribing exercise intensity.

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TABLE 1

Demographic and clinical characteristics of subjects at baseline.

Characteristic	All Patients in Analysis (N = 767)
Age (yr), median (25th–75th percentile)	57 (49–66)
Female, n (%)	227 (30)
Race, n (%)	
White	445 (59)
Black	265 (35)
Other	48 (6)
Resting systolic blood pressure (mmHg), median (25th–75th percentile)	112 (102–128)
Resting diastolic blood pressure (mmHg), median (25th–75th percentile)	70 (62–80)
Resting seated HR before exercise test (beats•min <sup>-1</sup> ), median (25th–75th percentile)	69 (61–77)
Weight (kg), median (25th–75th percentile)	91 (77–108)
Body mass index (kg•m <sup>-2</sup> ), median (25th–75th percentile)	30 (26–36)
Left ventricular ejection fraction (%), median (25th–75th percentile)	25 (21–31)
History of diabetes, n (%)	251 (33)
History of stroke, n (%)	68 (9)
History of hypertension, n (%)	454 (60)
Etiology of HF, ischemic, n (%)	375 (49)
New York Heart Association Functional Class, n (%)	
II	557 (73)
III/IV	210 (27)
Number of HF hospitalizations in previous 6 months, n (%)	
0	568 (74)
1	152 (20)
2+	42 (5)
Peak exercise HR (beats•min <sup>-1</sup> ), median (25th–75th percentile)	125 (111–140)
Peak oxygen uptake (mL•kg <sup>-1</sup> •min <sup>-1</sup> ), median (25th–75th percentile)	15.7 (12.5–19.0)
Peak RER, median (25th–75th percentile)	1.13 (1.09–1.19)
Peak RPE (Borg, 6–20), median (25th–75th percentile)	17 (15–19)
Prior coronary artery bypass graft surgery, n (%)	154 (20)
Prior percutaneous coronary intervention, n (%)	161 (21)
Prior myocardial infarction, n (%)	318 (41)
History of atrial fibrillation/flutter, n (%)	71 (9)
History of peripheral vascular occlusive disease, n (%)	39 (5)
History of depression, n (%)	152 (20)
Angiotension-converting enzyme inhibitor, n (%)	584 (76)
Dose of $\beta$ -adrenergic blocking agent, carvedilol equivalents (mg•d <sup>-1</sup> ), median (25th–75th percentile)	40 (25–50)

TABLE 2

Full predictive model for maximal HR.

Variable	Parameter Estimate	P	Partial R <sup>2</sup>
Resting HR (beats•min <sup>-1</sup> )	0.6	<0.0001	0.135
Age (yr)	-0.5	<0.0001	0.109
New York Heart Association Functional Class, for III/IV vs II	-8.3	<0.0001	0.044
Prior myocardial infarction	-6.0	<0.0001	0.026
History of diabetes	-5.5	<0.0001	0.020
Dose of $\beta$ -adrenergic blocking agent, carvedilol equivalents (mg•d <sup>-1</sup> )	-0.01	<0.0007	0.015
Modality for exercise testing, for stationary cycle vs. treadmill	-6.5	0.0015	0.013

Model R<sup>2</sup> = 0.36; SEE = 17 beats•min<sup>-1</sup>.

TABLE 3

Six candidate equations for estimating maximal HR on  $\beta\text{B}$  therapy.

Model Type	Equation No.	Equation Type	Equation	R <sup>2</sup>	SEE
Two-variable predictor using resting HR and age	1	Regression <sup>a</sup>	$120.22 + 0.57 (\text{resting HR}) - 0.6 (\text{age}) - 5.2 (\text{if bike test})$	0.28	18
	2	Simplified	$119 + 0.5 (\text{resting HR}) - 0.5 (\text{age}) - 5 (\text{if bike test})$	0.28	18
One-variable predictor using resting HR	3	Regression <sup>a</sup>	$75.12 + 0.73 (\text{resting HR}) - 7.12 (\text{if bike test})$	0.17	20
	4	Simplified	$91 + 0.5 (\text{resting HR}) - 7 (\text{if bike test})$	0.15	20
One-variable predictor using age	5	Regression <sup>a</sup>	$168.35 - 0.76 (\text{age})$	0.19	19
	6	Simplified	$159 - 0.5 (\text{age})$	0.17	20

<sup>a</sup>The equation contains the parameter estimate(s) when the specific predictor are fit in a linear regression model without other predictors.

**TABLE 4**

Estimated maximal HR using a two-variable simplified equation for patient on  $\beta\text{B}$  therapy.<sup>a</sup>

Age (yr)	Resting HR (beats•min <sup>-1</sup> )															
	50	54	58	62	66	70	74	78	82	86	90	94	98	102	106	110
40	124	126	128	130	132	134	136	138	140	142	144	146	148	150		
42	123	125	127	129	131	133	135	137	139	141	143	145	147	149		
44	122	124	126	128	130	132	134	136	138	140	142	144	146	148		
46	121	123	125	127	129	131	133	135	137	139	141	143	145	147		
48	120	122	124	126	128	130	132	134	136	138	140	142	144	146		
50	119	121	123	125	127	129	131	133	135	137	139	141	143	145		
52	118	120	122	124	126	128	130	132	134	136	138	140	142	144		
54	117	119	121	123	125	127	129	131	133	135	137	139	141	143		
56	116	118	120	122	124	126	128	130	132	134	136	138	140	142		
58	115	117	119	121	123	125	127	129	131	133	135	137	139	141		
60	114	116	118	120	122	124	126	128	130	132	134	136	138	140		
62	113	115	117	119	121	123	125	127	129	131	133	135	137	139		
64	112	114	116	118	120	122	124	126	128	130	132	134	136	138		
66	111	113	115	117	119	121	123	125	127	129	131	133	135	137		
68	110	112	114	116	118	120	122	124	126	128	130	132	134	136		
70	109	111	113	115	117	119	121	123	125	127	129	131	133	135		
72	108	110	112	114	116	118	120	122	124	126	128	130	132	134		
74	107	109	111	113	115	117	119	121	123	125	127	129	131	133		
76	106	108	110	112	114	116	118	120	122	124	126	128	130	132		
78	105	107	109	111	113	115	117	119	121	123	125	127	129	131		
80	104	106	108	110	112	114	116	118	120	122	124	126	128	130		

<sup>a</sup>Estimated maximal HR = 119 + 0.5 (resting HR) - 0.5 (age);  $R^2 = 0.28$ ; SEE = 18; subtract 5 beats•min<sup>-1</sup> if test is completed using a cycle ergometer.