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Chronotropic Incompetence: Causes, Consequences, and Management

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Introduction

Chronotropic incompetence (CI), broadly defined as the inability of the heart to increase its rate commensurate with increased activity or demand, is common in patients with cardiovascular disease, produces exercise intolerance which impairs quality-of-life, and is an independent predictor of major adverse cardiovascular events and overall mortality. However, the importance of CI is under-appreciated and CI is often overlooked in clinical practice. This may be due partly due to multiple definitions, the confounding effects of aging, medications, and the need for formal exercise testing for definitive diagnosis. This review discusses the definition, mechanisms, diagnosis, and treatment of CI, with particular emphasis on its prominent role in HF. CI is common, can be diagnosed by objective, widely available, inexpensive methods, is potentially treatable, and its management can lead to significant improvements in exercise tolerance and quality-of-life.

Contribution of Heart Rate to Exercise Performance

The ability to perform physical work is an important determinant of quality-of-life and is enabled by an increase in oxygen uptake (VO_2). During maximal aerobic exercise in healthy humans, VO_2 increases approximately 4-fold. This is achieved by 2.2-fold increase in heart rate (HR), a 0.3-fold increase in stroke volume, and a 1.5-fold increase arteriovenous oxygen

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difference. Thus, the increase in HR is the strongest contributor to the ability to perform sustained aerobic exercise. It is therefore not surprising that CI can be the primary cause or a significant contributor to severe, symptomatic exercise intolerance.

Heart Rate Control

Heart rate at any moment in time reflects the dynamic balance between the sympathetic and parasympathetic divisions of the autonomic nervous system. Although the intrinsic rate of depolarization of the SA node is a 100 min, resting HR in humans is generally much lower (60-80 b/min) due to the predominating influence of the parasympathetic nervous system efferent Vagus nerve. Increased resting HR levels, due to increased sympathetic and/or decreased parasympathetic “tone”, have been associated with increased cardiovascular death, ischemic heart disease, and sudden cardiac death in both asymptomatic men and women.; Furthermore, a resting HR ≥ 70 b/min has been associated with increased mortality in a patients with stable coronary artery disease and left ventricular (LV) dysfunction.;

An intact HR response is vital for tightly matching a subject's cardiac output to their metabolic demands during exertion. Failure to achieve maximal HR, inadequate submaximal HR, or HR instability during exertion are all examples of impaired chronotropic response. These conditions are relatively common in patients with sick sinus syndrome, atrioventricular block, coronary artery disease, and heart failure (HF).

Immediately after the termination of exertion, sympathetic withdrawal and increased parasympathetic tone to the SA node combine to cause a rapid decline in HR. A delayed recovery of HR after exertion has been associated with increased all-cause mortality risk in a variety of asymptomatic and diseased populations, even after adjusting for severity of cardiovascular disease, LV function, and exercise capacity. While there are a number of methods of evaluating HR recovery, the most widely used threshold for increased risk of all-cause mortality has been a decrease in HR from peak exercise to 1 minute of passive supine recovery of < 12 b/min (or < 18 b/min if recovery was “active” i.e. unloaded cycling or slow walking) and/or a decrease in HR from peak exercise to 2 minutes of recovery of < 42 b/min.

In contrast, highly trained athletes often display a rapid and profound drop in HR of 30-50 beat during the 1st minute of recovery from strenuous exertion. The rate and magnitude of HR recovery after exertion appears to be directly related to level of parasympathetic tone. The association between early HR recovery and parasympathetic nervous system function was elegantly demonstrated in a study of three groups of subjects – athletes, normal subjects, and patients with HF. Among athletes and normal subjects, there was a biexponential pattern of HR during early recovery, with a steep non-linear decrease during the first 30 seconds followed by a more shallow decline (Figure 1A). When the same subjects were given atropine and exercise testing was repeated, the initial steep decrease in HR observed among athletes and normal subjects disappeared (Figure 1B).

In the the Framingham Offspring study, Nearly 3,000 healthy men and women were followed for an average of 15 years. Individuals in the top quintile of HR recovery at

1-minute after exercise had the lowest risk of coronary heart disease and cardiovascular disease (hazard ratios of 0.54 and 0.61, respectively) compared to those in the lower 4 quintiles of HR recovery. The MRFIT study also demonstrated that a delayed HR recovery (<50 beats after 3 minutes) was an independent predictor of all-cause death in asymptomatic men. In a long-term, 23 year follow-up study of asymptomatic working men who underwent exercise stress testing, factors independently associated with increased risk of fatal myocardial infarction, were a resting HR more than 75 beats/min, an increase in HR from rest to peak exercise of less than 89 beats/min and a decrease in HR of less than 25 beats after the cessation of exercise. In conclusion, the autonomic imbalance of sympathetic and parasympathetic activity, observable through HR responses at rest as well as during and after exercise, is strongly associated with increased risk of adverse cardiovascular outcomes and sudden death.

Effect of age and gender on the HR response to exercise

There is no change in resting HR with adult aging. However, in healthy humans, there is a marked age-related decrease in maximum heart rate in response to exercise that is inexorable, highly predictable, and occurs in other mammalian species as well as humans.;; The age-related decline in maximal HR is the most substantial age-related change in cardiac function, both in magnitude and consequence.;; It is primarily responsible for the age-related decline in peak aerobic exercise capacity.;; Starting from early adulthood, maximal heart rate declines with age at a rate of ~ 0.7 beats min^{-1} year^{-1} in healthy sedentary, recreationally active and endurance exercise-trained adults.. Though its mechanism(s) are not fully understood, dual-blockade studies show that intrinsic HR declines by 5-6 beats per minute for each decade of age such that resting HR in an 80 year old is not much slower than the intrinsic HR. This indicates that at rest there is minimal parasympathetic tone. In support of this, the increase in HR after atropine in an older person is less than half that in the young. There are also significant alterations in the sympathetic influence on heart rate response to exercise in aging, with increased circulating catecholamines and reduced responsiveness. Doses of isoproterenol that increase HR by 25 b/min in young healthy men produce an increase of only 10 b/min in older persons.

The normal, age-related decline in maximal HR during exercise is not significantly modified by vigorous exercise training, suggesting that it is not due to the age-related decline in physical activity level. Also, it does not appear to be due to inadequate sympathetic stimulation, since both as serum norepinephrine and epinephrine are increased rather than decreased at rest in healthy elderly. Further, with exertion or stress, catecholamines increase even more than in young persons under the same stress conditions.

The traditional equation to predict maximal HR ($220 \text{ b/min} - \text{age}$), was developed based on studies primarily in middle-aged men, some of whom had known coronary artery disease and were taking beta-blockers.;; This equation has been associated with tremendous inter-subject variability with a standard deviation of ± 11 b/min that equation increases to ± 40 b/min in patients with coronary heart disease receiving beta blockers. Consequently an alternative formula from Tanaka et al ($208 - 0.7 \times \text{age}$) is becoming more accepted for

determining age-predicted maximal HR (APMHR) even though it may still under-predict APMHR in older adults (Figure 2).

Several earlier studies suggested that gender affected the heart rate trajectory during exercise and recovery, and that the traditional equation (220-age) overestimates maximal heart rate in younger women but underestimates in older women.; A meta-analysis indicated that maximal HR was unaffected by gender. A recent, large prospective study in over 5,000 asymptomatic women showed that the traditional equation significantly overestimates maximal HR and thus proposed a new equation where; maximal HR=206–0.88(age).

Brawner et al. demonstrated that the 220 – age equation is not valid in patients with coronary heart disease (CHD) taking beta-adrenergic blockade (β B) therapy and developed the equation; [164-0.7(age)] for this population.

All of aforementioned studies improve on the estimations of maximal heart rate versus the traditional 220-age approach, but still produce substantial standard error of estimates (10-22 beats/min). Given the inherent variability in maximal heart, regression equations using a single predictor variable, such as age, are unlikely to be 100% accurate, and increasing the number of predictor variables adds little improvement and reduces practicality for clinical use. Thus, for estimating predicted maximal heart rate, we suggest selecting an equation that was generated in a population that most closely matches the population of interest. In this regard, the equation of Tanaka et al is recommended for apparently healthy persons, and the equation of Brawner et al is recommended for those with known or suspected cardiovascular disease. While these also are imperfect, they are superior to the traditional “220-age” equation and are practical.

Definition, Criteria, and Measurement of CI

A barrier to progress in studies of CI and its clinical management has been a lack of consistent methodology for determining CI. The lack of standardized criteria likely accounts for the wide range in reported prevalence of CI (9-89%) in the literature.- In an evaluation of more than 1,500 CI patients referred for pacemaker implantation, the use of 5 different definitions of CI resulted in a prevalence of CI of 34-87%. CI has been most commonly diagnosed when HR fails to reach an arbitrary percentage (either 85%, 80% or less commonly, 70%) of the age-predicated maximal HR (usually based on 220-age equation described earlier) obtained during an incremental dynamic exercise test.- CI has also been determined from change in HR from rest to peak exercise during an exercise test, commonly referred to as the HR reserve. Since the proportion of actual HR achieved during exercise depends in part on the resting HR level, the chronotropic response to exercise can also be assessed as the fraction of HR achieved at maximal effort. Thus, adjusted HR reserve, determined from the change in HR from rest to peak exercise divided by the difference of the resting HR and the age-predicated maximal HR has been commonly used. The majority of studies in the literature have used failure to obtain 80% of the HR reserve, obtained during a graded exercise test, as the primary criteria for CI.

However, before concluding that a patient has CI, it is important to consider their level of effort and reasons for terminating the exercise test. Patients should be encouraged to continue on the exercise modality until a true symptom-limited (exhaustive) maximal levels are achieved. Symptoms and subjective ratings of perceived exertion (RPE) can provide an estimate of exertion level, and is an acceptable method. Respiratory exchange ratio (RER, i.e. volume of carbon dioxide produced/volume of oxygen consumed) obtained from expired respiratory gas analysis at peak exertion during the exercise test, is the most definitive, objective, clinically available measure of physiologic level of effort during exercise. RER is reliable, and while requires expired gas analysis equipment, current generation equipment is automated and is moderate in cost. RER is a continuous variable, ranging from <0.85 at quiet rest to > 1.20 during intense, exhaustive exercise. Higher RER values indicate increasing confidence of maximal effort. It is generally accepted that an RER < 1.05 at peak exercise suggests submaximal effort or that the test was terminated prematurely and should lead to caution in diagnosing CI.

Wilkoff et al utilized the expired gas analysis technique to more objectively evaluate CI using the relationship between HR and VO_2 during exercise. In this approach, the metabolic-chronotropic relationship (MCR) (also known as the chronotropic index) is calculated from the ratio of the HR reserve to the metabolic reserve during submaximal exercise. The advantage of using the MCR is that it adjusts for age, physical fitness, and functional capacity and it appears to be unaffected by the exercise testing mode or protocol. In normal adults, the percentage of HR reserve achieved during exercise equals the percentage of metabolic reserve achieved. This physiologic concept allows for a single HR achieved at any point during an exercise study (HR_{stage}) to be determined as consistent or inconsistent with normal chronotropic function. This is accomplished by using the following formula, where $\text{METs} = \text{VO}_2 \text{ in ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} / 3.5$:

$$\text{HR}_{\text{stage}} = [(220 - \text{age} - \text{HR}_{\text{rest}})] \times (\text{METs}_{\text{stage}} - 1) / (\text{METs}_{\text{peak}} - 1) + \text{HR}_{\text{rest}}$$

. The Wilkoff model predicts the MCR slope of the normal sinus response to be 1.0 with a 95% confidence interval between .8 and 1.3. An MCR slope or any single MCR value (from one stage) of ≤ 0.80 is considered indicative of CI.

Consequently, the information that should be recorded for each patient during an exercise test to evaluate CI includes: age; resting HR (HR_{rest}); age-predicted maximal HR (APMHR) = $220 \text{ b/min} - (\text{patient's age})$; age-predicted HR reserve (APHRR) = $(\text{APMHR}) - (\text{HR}_{\text{rest}})$; observed maximal HR during exercise test (HR_{max}); oxygen consumption ($\text{VO}_2 = \text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) at each stage and at peak effort; and RER. For example, in a 60 year old subjects who only achieved an RER of 0.96 at peak exertion (i.e. submaximal effort!), entering following data from a submaximal stage (25 watts) of exercise ($\text{HR}_{\text{rest}} = 67$; $\text{HR}_{\text{peak}} = 100$, $\text{HR}_{@25\text{w}} = 97$, $\text{MET}_{@25\text{w}} = 3.3$, $\text{MET}_{\text{peak}} = 3.7$. into Wilkoff equation would result in a CI index = .66 (actual HR_{stage} of 97/estimated HR_{stage} of 147) which is well below the CI cut-off of .80. The Wilkoff approach can be combined with other methods to determine the presence of CI in challenging situations: 1) if despite reaching a peak exercise RER of greater than 1.05 (suggesting adequate effort), the patients fails to achieve a HR_{max} 80-85% of APHRR

(or 80-85% HR reserve); 2) if respiratory exchange ratio does not reach 1.05 (suggesting submaximal effort) an MCR relationship of < 0.80 can be used.

While a variety of exercise testing protocols (Bruce, RAMP, etc) and modes of testing can be employed, a specific CI exercise testing protocol has been employed in some laboratories and evaluates the MCR relationship from two stages on a treadmill protocol (stage 1 = 1.3 mph & 0.5% grade and stage 2 = 3.0 mph & 1.5% grade). The process of data collection and analysis described above is subsequently used to determine the adequacy of the chronotropic responses.

Savonen et al; have proposed methods attempting to separate the effects of parasympathetic withdrawal versus sympathetic stimulation on the HR response to exercise. This is based on the physiological observations that found that the HR increase below 100 b/min is predominantly controlled by gradual withdrawal of parasympathetic tone, whereas from 100 b/min to maximum, the HR increase is predominantly the result of increasing sympathetic nervous system activity. Savonen et al have termed this a “delineational” approach. Their work indicates that in men with and without coronary heart disease, an increase in HR from 40-100% of maximal work capacity in the exercise test predicts mortality and acute myocardial infarction better than the peak HR or HR reserve approaches. Similarly, another study demonstrated that a blunted HR increase from rest to 33% of maximal work capacity was not as strong of a predictor of death as a low HR reserve in patients referred for exercise testing. While provocative, these innovative approaches for assessing chronotropic response to exercise will require further validation before clinical application.

Effect of Medications and other Confounding Influences on CI

A number of commonly used cardiovascular medications including, beta blockers, digitalis, certain calcium channel blockers, amiodarone, and others can confound the determination of CI.; Beta-blockers may result in pharmacological induced CI and obscure identification of an underlying intrinsic abnormality in neural balance. In one study a suitable threshold for CI among HF patients using beta blockers was found to be 62% of APHRR. Using this lower HR threshold, CI was able to be reliably identified and was an independent predictor of death. These modified criteria have been utilized to design clinical trials. Care should be taken before applying the modified threshold criteria to ensure that the patient is on a non-trivial dose and is compliant with the medication.

The use of separate CI criteria for patients taking beta blocker medications has been challenged by other studies that failed to demonstrate that any effect on beta blockers, including at high dose, on the occurrence of CI. Figure 3 shows the similar relationship between HR reserve and VO_2 peak in HF patients that are either taking or not taking beta blockers. Similarly, Jorde and colleagues examined the relationship between exercise time and HR during treadmill exercise testing in HF patients. As seen in Figure 4, the HR slope is abnormal in HF patients with CI, yet beta blockers have no impact on this relationship in these patients. While still an evolving concept, chronic treatment of HF patients with beta blockers may paradoxically improve chronotropic response by decreasing sympathetic tone and/or by increasing beta receptor activity.

Chronic atrial fibrillation confounds the assessment of CI and criteria for its diagnosis have not been established. Exercise testing can be used to assess adequacy of response following pacemaker insertion for CI. Intrinsic HR response can be assessed in patients with existing pacemakers by reprogramming or suspending the device with a magnet, taking care to ensure the patient is not completely pacemaker dependent beforehand.

Relationship between Chronotropic Incompetence and Mortality

The relationship between CI and increased cardiac and all-cause mortality was first reported more over 30 years ago by Hinkle et al. He described a group of men who were unable to reach an expected HR on a standard exercise protocol and who subsequently experienced increased frequency of cardiac events during 7 year follow-up. These investigators initially termed this inadequate HR response a “sustained relative bradycardia”. Subsequently, Rubinstein et al and Eckberg et al described a relationship between this phenomenon and autonomic dysfunction. Ellestad et al confirmed the finding increased risk of cardiac events during long-term follow-up, and showed that the risk of cardiac events associated with an abnormal HR response during exercise was greater than that associated with ischemic ST segment depression. He suggested the term “chronotropic incompetence” to describe this abnormal HR response during exercise.

Subsequently, a number of studies, expanded on these findings and reported that an attenuated HR response to exercise is predictive of increased mortality and coronary heart disease risk, independent of a variety of other confounding factors, including age, gender, physical fitness, traditional cardiovascular risk factors, and ST-segment changes during exercise.;;; In over 5,000 asymptomatic women, those with peak exercise HR > 1 SD below the predicted mean had markedly increased mortality during long-term follow-up (Figure 5). An attenuated HR response was found to be predictive of myocardial perfusion defects. A combination of CI and a myocardial perfusion defect during exercise stress testing carried a particularly high risk group of patients as potential candidates for heightened treatment. The prognostic value of an impaired HR response to exercise appears to persist even after considering the adverse effects of coronary artery disease and/or LV dysfunction.

In another study of 3,221 patients who underwent treadmill exercise echocardiography with a median follow-up of 3.2 years, failure to achieve 85% of maximal predicted HR was associated with increased mortality and cardiac death even after adjusting for LV function and exercise-induced myocardial ischemia. Azarbal et al showed that a low % HR reserve was a superior predictor compared to an inability to achieve 85% of APMHR as the later method identified 2.2 times more individuals at increased risk of cardiac death. An attenuated HR response to exercise also predicts major adverse cardiac events among persons with known or suspected cardiovascular disease. Furthermore, in HF patients not taking beta blockers, the presence of CI appears to increase mortality risk.

Thus, the HR profiles both during and after exercise are strong predictors of sudden death in asymptomatic and selected clinical populations, including those with coronary artery disease or HF. Collectively these findings provide the rationale for increased screening for

inappropriate/inadequate HR responses during exercise testing and recovery to assist with more effective risk stratification and prognosis.

Mechanisms of Exercise Intolerance in HF

In contrast to most other forms of heart disease, the incidence of HF, a debilitating disorder, is increasing with 500,000 new cases in the U.S. per year and a 175% increase in the number of hospital discharges for HF over the past 20 years. It has been shown that a majority of persons with HF living in the community have a preserved LV EF.- A hallmark characteristic of chronic HF, either HFrEF or HFpEF, is a markedly reduced capacity for physical exertion, with a subsequent reduction in VO_2 peak that is 15-40% below that age-matched controls. Work from our group and other has shown that patients with HFpEF have similar reductions in exercise tolerance measured as peak exercise oxygen consumption (VO_2 peak), have reduced submaximal exercise measures, ventilatory anaerobic threshold, 6 minute walk distance, quality-of-life, and markers of prognosis including VE/VCO_2 slope as those with HF with reduced EF (HFrEF).- These findings have been replicated by Smart, et al and others.

According to the Fick equation, an appropriate increase in VO_2 peak during exertion is dependent on both an increase in cardiac output as well as concomitant widening of the arterial-venous oxygen content difference.; The latter is related to abnormalities of skeletal muscle and vascular function that limit exercise intolerance associated in HF.; In addition, patients with HF often achieve less than 50% of the maximal cardiac output achieved by healthy individuals at peak exercise. The impairment in cardiac output response of HF patients correlates significantly with reductions in VO_2 peak. The reduced cardiac output response of HF is often attributed to an attenuated stroke volume, subsequent to either systolic and/or diastolic LV dysfunction. Stroke volume, already diminished at rest in the HF patient subsequent to systolic and/or diastolic abnormalities, rises only modestly to a peak of 50-65 ml versus 100 ml in healthy subjects. Consequently, HF patients must rely to a greater extent on increases in HR to augment cardiac output to compensate for their inadequate stroke volume during physical exertion. Whereas maximal HR during exercise may be only mildly reduced at peak exertion, HR reserve (i.e. degree of HR augmentation above resting levels) is often blunted more substantially in HF patients due to the sympathetically-driven elevation in resting HRs.

Contribution of Impaired HR Response to Exercise Intolerance in HF

As previously described, the Fick equation dictates that an increase in cardiac output during exertion is dependent on an increase in stroke volume and/or HR. In HFrEF and HFpEF patients, the primary limiting factor during exertion is generally assumed to be an inability to increase the stroke volume commensurate with degree of effort. Yet given the potential impact of HR responsiveness on cardiac output and subsequently VO_2 peak, it is surprising there has not been more interest on CI in a patient population where exercise intolerance is so problematic. We recently demonstrated that in a group of 102 elderly patients with either HFrEF or HFpEF, that HR reserve (the difference between resting and peak HR achieved on bicycle exercise test) was significantly correlated ($r = .40$) with VO_2 peak (Figure 6).

Moreover, these findings indicated that the increase in HR during exercise accounts for an appreciable portion (i.e. 15%) of the observed differences in VO_2 peak in these older HF patients. This means that in a patient population with an average VO_2 peak of $14 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, abnormal HR accounts for about $2 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ($\pm 16\%$) in $\text{VO}_{2\text{peak}}$, and therefore has significant functional and prognostic ramifications.

Similarly, Witte et al found using $< 80\%$ of either APMHR or HR reserve, the average VO_2 peak was significantly lower ($- 2.6 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} = 14\%$ and $- 4.6 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} = 25\%$, respectively) in HFrEF patient with CI verses those without CI. Furthermore, Witte et al reported a correlation between VO_2 peak and delta HR (peak exercise HR – rest HR) of .56 and .60 for beta-blocked and non-beta blocked HF patients further supporting the significance and impact of inadequate HR increase during exertion in this population.

Borlaug et al evaluated parameters of exercise tolerance in HFpEF patients versus a control group without HF but matched on age, gender, important co-morbidities, and LV hypertrophy (controls). At peak exertion, the HFpEF patients had significant reductions in VO_2 peak (9.0 ± 3.4 vs $14.4 \pm 3.4 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, respectively) and HR (87 ± 20 vs. 115 ± 22 beats/min, respectively) compared to controls. Exercise capacity, expressed as VO_2 peak, correlated directly with cardiac output but was primary determined by HR and afterload responses during exercise. In contrast, change in end-diastolic volume and stroke volume were not correlated with exercise capacity. Furthermore, HFpEF patients had a slower HR rise, lower peak exercise HR, and impaired HR recovery, indicating abnormal autonomic function in these patients (Figure 7).

Prevalence of CI in HF

The reported prevalence of CI within the HF population has varied considerably with a range of 25-70%. This substantial variability is likely influenced by the criteria employed to determine CI as well as differing patient characteristics (age, disease severity, type/dose medications). In one of the earliest papers to evaluate the prevalence of CI in HF, Clark and Coates, using $< 80\%$ of APMHR as the criteria, found that approximately 28% of stable, non beta-blocked systolic HFrEF patients (mean age = 59) demonstrated CI. In contrast, Roche et al, using achievement of $\approx 80\%$ of APHRR as predetermined criteria, determined that 14 of 21 (66%) of stable, non beta-blocked, HFrEF patients (mean age 54 ± 10 yrs) demonstrated CI. Furthermore, Roche et al found no significant difference in age, HR, peak oxygen uptake or LV ejection fraction between patient with and without CI. In a slightly older group of HFrEF patients, Witte et al found that 103 of 237 (43%) HF patients met the criteria of $< 80\%$ of APMHR whereas 170 of 237 (72%) met the criteria of $< 80\%$ of APHRR. Witte et al did indicate that patients taking beta blockers were more likely to have CI than those not taking beta blockers when $< 80\%$ APMHR was used (49 vs. 32%, respectively) or $< 80\%$ APHRR was used (75 vs. 64%, respectively). In contrast, the criteria of $\approx 62\%$ APHRR is used for HF patients on beta blocker therapy, a significantly smaller percentage (22%) of patients were identified with CI.

We evaluated the prevalence of CI in older (> 60 yrs) HFrEF and HFpEF as well as in age-matched healthy subjects using $\approx 80\%$ of APMHR and the Wilkoff approach. While CI

was uncommon in healthy older adults (just 2 out of 28 subjects = 7%), the prevalence of CI was relatively similar between older HFrEF (12 of 46 = 26%) and HFpEF (11 of 56 = 19%). A more recent unpublished analysis of 207 older HFpEF patients, tested in our lab indicated that 28% of these patients met the CI criteria as described earlier. Phan et al has also observed abnormal HR responses to exercise in HFpEF patients versus age-matched hypertensive and healthy control subjects. Using the criteria of <80% APMHR, Phan et al. observed a similar prevalence of CI among HFpEF of 35. Like other studies employing multiple criteria, the prevalence of CI increased to 63% of HFpEF patients when 80% of HR reserve criteria was employed as the definition of CI. Consequently, in addition to the central and peripheral pathophysiological derangements observed in HF patients, a significant portion (one-third or more depending on criteria employed) of both HFrEF and HFpEF populations also have to significant CI contributing to their exercise intolerance.

Mechanisms of CI in HF

Studies in the 1980s by Bristow et al and Colucci et al were the first to associate CI in HF with down-regulation of beta receptors and desensitization in the presence of increased circulating catecholamine levels. Bristow and colleagues found a 50% or more reduction in beta-adrenergic receptor density in the LV myocardium of failing hearts explanted during transplant surgery. Colucci et al demonstrated that norepinephrine infusion results in a reduced HR response in HF patients versus healthy subjects. During maximal isoproterenol stimulation, Bristow et al observed a 45% reduction compared to normal in adenylate cyclase elaboration and up to 73% reduction in muscle contraction. These findings suggest that in HF patients, a decrease in beta-receptor density leads to a diminished sensitivity of the beta-adrenergic pathway and decrease in beta-agonist stimulated muscle contractility. Samejima et al demonstrated that the ratio of change in HR to change in log of norepinephrine ($\Delta \text{HR}/\Delta \log \text{NE}$), an index of sinoatrial node sympathetic responsiveness, decreased progressively with the severity of HF. Furthermore, the $\Delta \text{HR}/\log \Delta \text{NE}$ ratio during exercise was significantly correlated with anaerobic threshold, VO_2 peak, and VE/VCO_2 slope. An electrophysiology study of symptomatic HFrEF patients and age-matched normal subjects undergoing radiofrequency ablation for AV tachycardia or AV nodal tachycardia demonstrated that when compared to non-HF subjects, HF patients with no prior atrial arrhythmias have significant sinus node remodeling characterized by (1) anatomical and structural changes along the crista terminalis, (2) prolonged sinus node recovery and sinoatrial conduction, and (3) caudal localization of the sinus node complex with circuitous propagation of the sinus impulse. This reduction in sinus node reserve appears to be responsible, at least in part, for the bradycardia and possibly the CI seen commonly in HF.

Management of CI in HF

Exercise training. In addition to many other health benefits, endurance exercise training in healthy individuals results in favorable changes in chronotropic function such as decreased resting and submaximal exercise HRs, as well as a more rapid decline in post-exercise HRs. Most of these HR adaptations appear to be related to alteration in the balance of sympathetic and parasympathetic influence of the autonomic nervous system. Moreover,

endurance exercise training generally improves exercise tolerance in HFrEF patients through a variety of potential central and peripheral mechanisms. The specific effects of exercise training on autonomic dysfunction and neurohormal activation in chronic HF include with increased baroreflex sensitivity and HR variability and reduced sympathetic outflow, plasma levels of catecholamines, angiotensin II, vasopressin, and brain natriuretic peptides at rest. Consequently, it appears that exercise training modifies the abnormal afferent stimuli from the failing heart that tend to increase sympathetic outflow, leading to autonomic derangement and neurohumoral activation. Moreover, Hasking et al found that plasma norepinephrine concentrations sampled during supine rest were increased in patients with asymptomatic LV dysfunction and increase further with the progression to overt HF; at the later stages of overt HF, total body spillover was on average double that of control subjects and norepinephrine clearance was reduced by a third. While beneficial, the specific mechanism responsible for modification of the neurohumoral activation and autonomic derangement in HF patients during exercise training is yet to be clarified.

Several exercise training studies have demonstrated that peak exercise HR increases 5-7% and contributes to the increase in cardiac output and VO_2 peak usually observed in HF patients with exercise training. In a meta-analysis of 35 randomized studies of exercise training HF patients indicated that peak HR increased by an average of 4 b/min or 2.5% of the pre-training level. Keteyian et al demonstrated that after 24 weeks of endurance exercise training, peak exercise HR increased by 7% (approximately 9 beats/min) yet remained unchanged in a non-exercise control group. Furthermore, the training-induced increase in peak HR accounted for 50% of the increase in VO_2 peak ($+2 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} = 14\%$) in the exercise training group. While alterations in beta-adrenergic receptor sensitivity may explain these findings, other mechanisms responsible for or contributing to the improved chronotropic response in HF patients cannot be excluded. Further information is needed regarding the impact of exercise training on the chronotropic response of HFrEF and HFpEF patients.

Rate adaptive pacing. There is a linear relationship between HR and VO_2 during exercise in a variety of patient populations, including HF, where a 2-6 beat/min increase in HR is associated with a $1 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ increase in VO_2 during exercise. Consequently, rate-adaptive pacing has been shown to enhance functional capacity in patients with an inadequate chronotropic response and those meeting formal definitions of CI.; Despite the potential to improve HR, cardiac output, and subsequently VO_2 during exertion in HF patients with chronotropic impairment, rate-adaptive pacing in this population has received minimal attention.; Furthermore, it may be counterintuitive for some clinicians to believe certain HF patients may benefit from a pacemaker particularly in the absence of bradycardiac/heart block.

The potential benefit of rate-adaptive pacing, in conjunction with cardiac resynchronization therapy, on exercise performance in HFrEF patients has been assessed by Tse et al. Twenty HFrEF patients with CI (defined as achieving $< 85\%$ APMHR and $< 80\%$ APHRR) with an implanted cardiac resynchronization device (> 6 months) underwent treadmill exercise testing with measurement of VO_2 . During the exercise testing, the cardiac resynchronization device was programmed to: 1) DDD mode with fixed AVI (DDD-off); 2) DDD mode with

AVI algorithm on (DDD-ON); and 3) DDDR mode. None of the 20 patients in the study achieved > 85% APMR and 11 (55%) failed to reach > 70% APMHR, a level indicative of severe CI. In the overall group, rate-adaptive pacing during cardiac resynchronization therapy increased peak exercise HR and exercise time but did not have an incremental benefit on peak exercise VO₂ peak. However, in the HF patients with more severe CI (those achieving < 70% APMHR), rate-adaptation significantly increased peak HR, exercise time, and VO₂peak. Further, in the majority (82%) of these patients, the improvement in chronotropic response with rate-adaptive pacing was associated with ~ 20% increase in VO₂peak.

It should be noted that for the majority of patients with less severe CI (those achieving 70-85% APMHR) there was little or no benefit, and one-third of the patients experienced a reduction in exercise capacity with rate-adaptive pacing. While it appears that rate-adaptive pacing has potential benefit in carefully selected patients with HFpEF, advances in this area are hindered by lack of standardized, accepted definitions and selection criteria. Furthermore, at this time it is unclear if CI is causal or simply a marker of advanced disease and if treating this with a pacemaker would improve functional status in HFpEF patients. Clearly, this issue requires further investigation in the future.

Even less is known regarding pacing in patients with HFpEF. The current RESET trial is designed to evaluate the effect of rate-adaptive pacing in HFpEF patients with overt CI. The rationale for this intervention is based on the observations that ~ 30 % of this population have CI and that impairment in chronotropic function contributes significantly to their objectively measured exercise intolerance. The outcomes of this randomized, controlled trial has the potential to help determine if rate-responsive pacing is an effective approach for improving exercise functional in this patient population.

Conclusions and Suggested Approach to Assessment and Management

Chronotropic incompetence is common, an important cause of exercise intolerance, and an independent predictor of major adverse cardiovascular events and mortality. It is present in up to 1/3 of patients with HF and contributes to their prominent exertional symptoms and reduced quality-of-life. Although the underlying mechanisms for CI in HF and other disorders are incompletely understood, available data suggest roles for reduced beta-receptor density and/or sensitivity secondary to increased sympathetic drive.

The diagnosis of CI should take into account the confounding effects of aging, physical condition, and medications, but can be achieved objectively with widely available exercise testing methods and standardized definitions. A three step approach to assessment is suggested. First, perform a progressive, exhaustive, symptom-limited exercise test. If practical, this should include automated expired gas analysis using a standard, commercially available system, for assessment of RER, which objectively verifies level of effort, and peak VO₂. Then, utilize a formula for peak heart rate that is relevant to the patient's profile. In general this will be the Tanaka formula for apparently healthy persons and the Brawner formula for those with cardiovascular disease or on beta-blockers. If the patient fails to achieve 80% of their APMHR on this test despite good/maximal effort (judged with RPE,

symptoms, and RER levels), then the Wilkoff Chronotropic Index should be calculated. If CI is found to be present, a search for potentially reversible causes is warranted.

In HF, beta-adrenergic blockade may have less detrimental effect on exercise capacity than previously thought, and may even paradoxically improve exercise performance. Beta blockers and other negative inotropes do not appear to have as a major impact on HR response to exercise in the HF patients and thus separate CI criteria for these patients does not appear necessary. Furthermore, it appear that beta blockers may not substantially increase the prevalence of CI in HF patients. The potential of more novel beta-blockers to reduce the prevalence of CI in HF patients is unclear.

While exercise training and rate-adaptive pacing have been shown to improve chronotropic responses and exercise capacity in HF, clearly more research is needed to fully evaluate the impact of these therapies on key clinical outcomes.

CI is a common, easily diagnosed, and potentially treatable cause of exercise intolerance and merits more attention by clinicians when they encounter patients with symptoms of effort intolerance.

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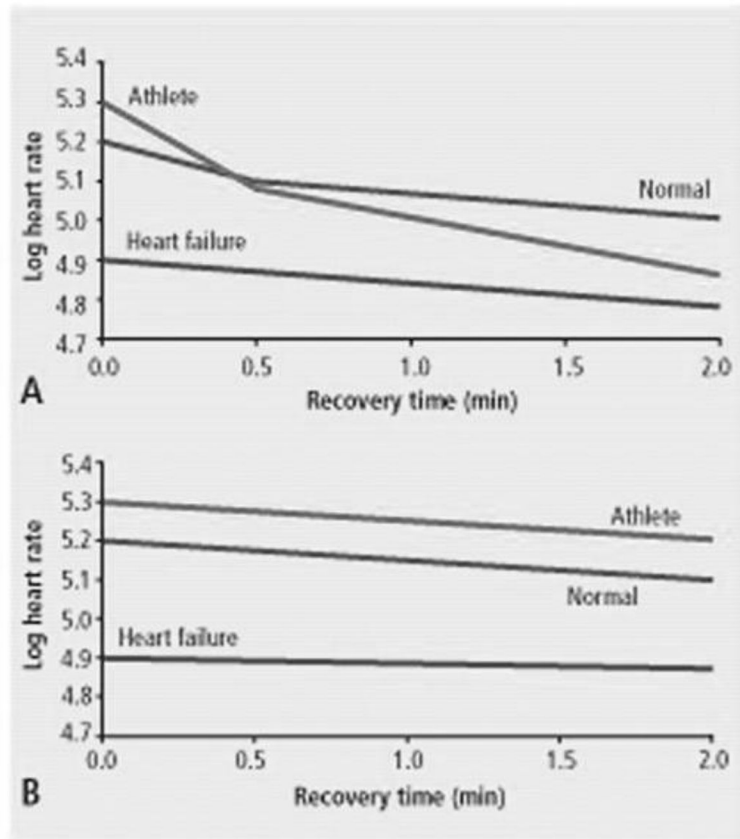


Figure 1. Influence of parasympathetic tone on heart rate recovery. A. Absolute heart rates (after log transformation) during the first 3 minutes after exercise in 3 groups of subjects. Among athletes and normal subjects, there is a biexponential relationship which is absent in heart failure patients. B. After atropine, the initial steep slope is absent. From Lauer MS, *Cleve Clin J of Med.* 2009;76:S18-S22.

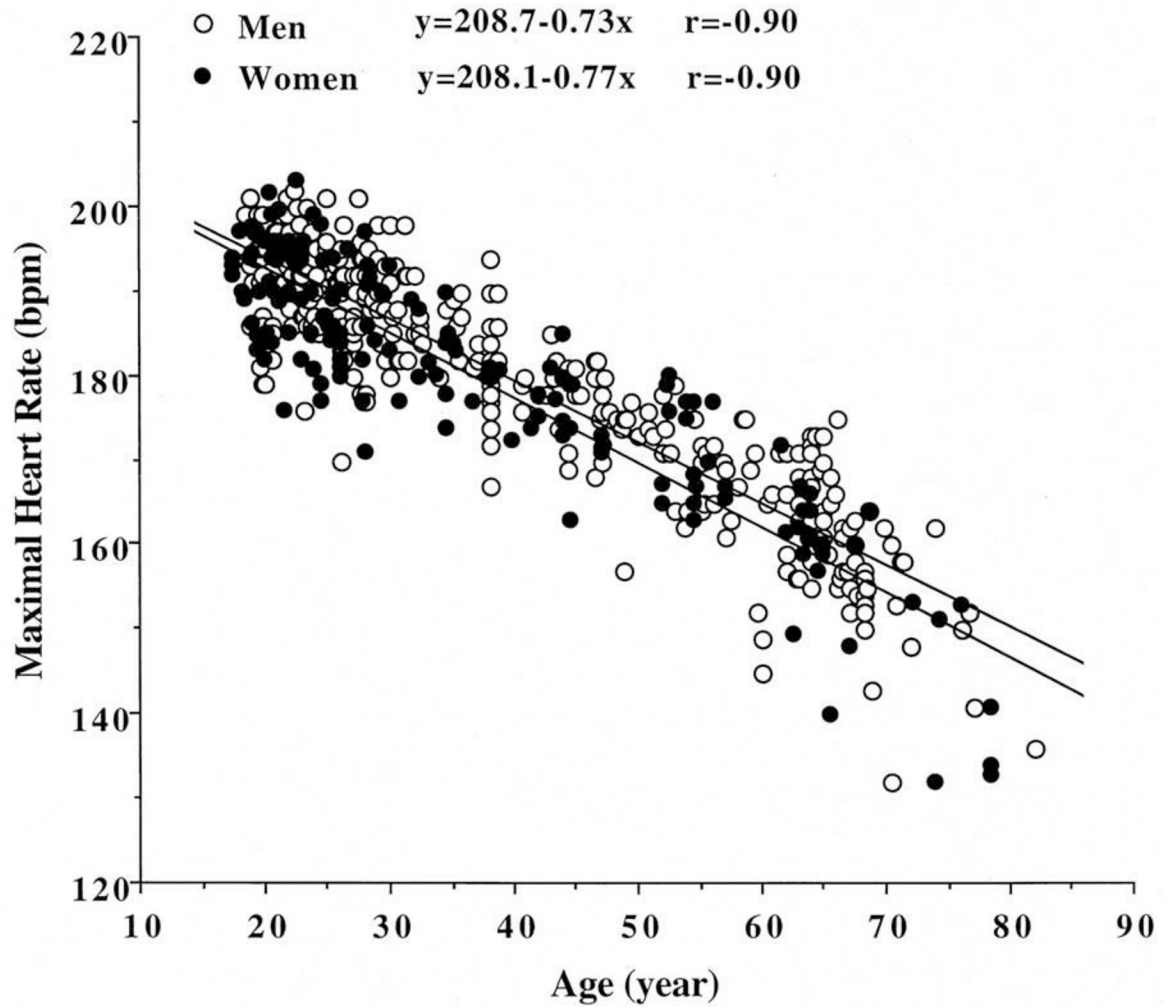


Figure 2. Relationship between age and maximal heart rate in over 5,000 asymptomatic women, with 95% confidence limits. From these data, a new prediction equation was proposed: peak heart rate = $206 - 0.88(\text{age})$. From Tanaka H, JACC 2001;37:153-156.

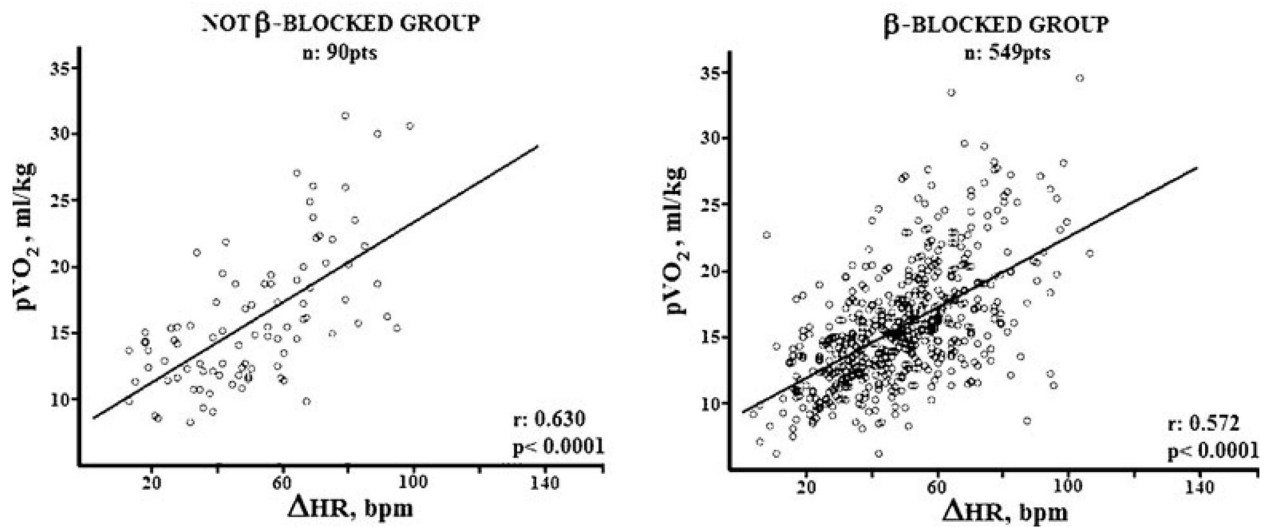


Figure 3.

There is a significant relationship between change in heart rate during exercise and VO₂peak in patients with HFREF, but there is no significant difference in this relationship between those patients taking beta-blockers versus not taking them. From Magri et al; Cardiovascular Therapeutics 2010; In press.

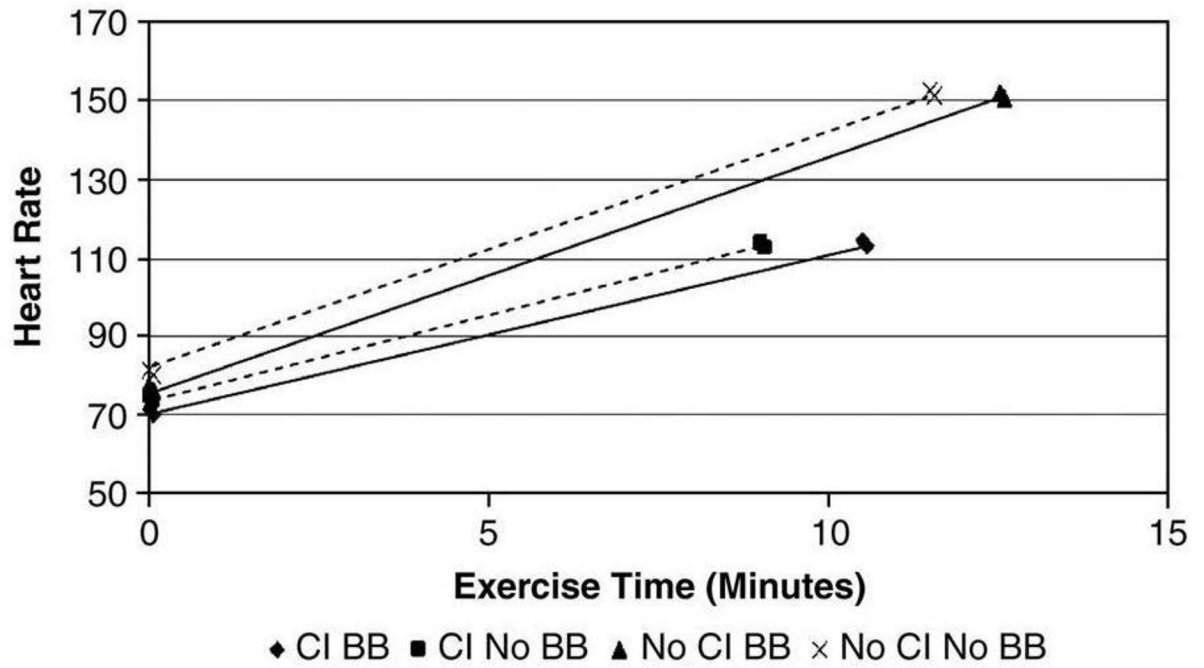


Figure 4. In patients with HF, beta blockers do not significantly impact the relationship between heart rate and exercise time, regardless of whether CI is present. From Jorde et al; European J of Heart Failure 2008;96-101.

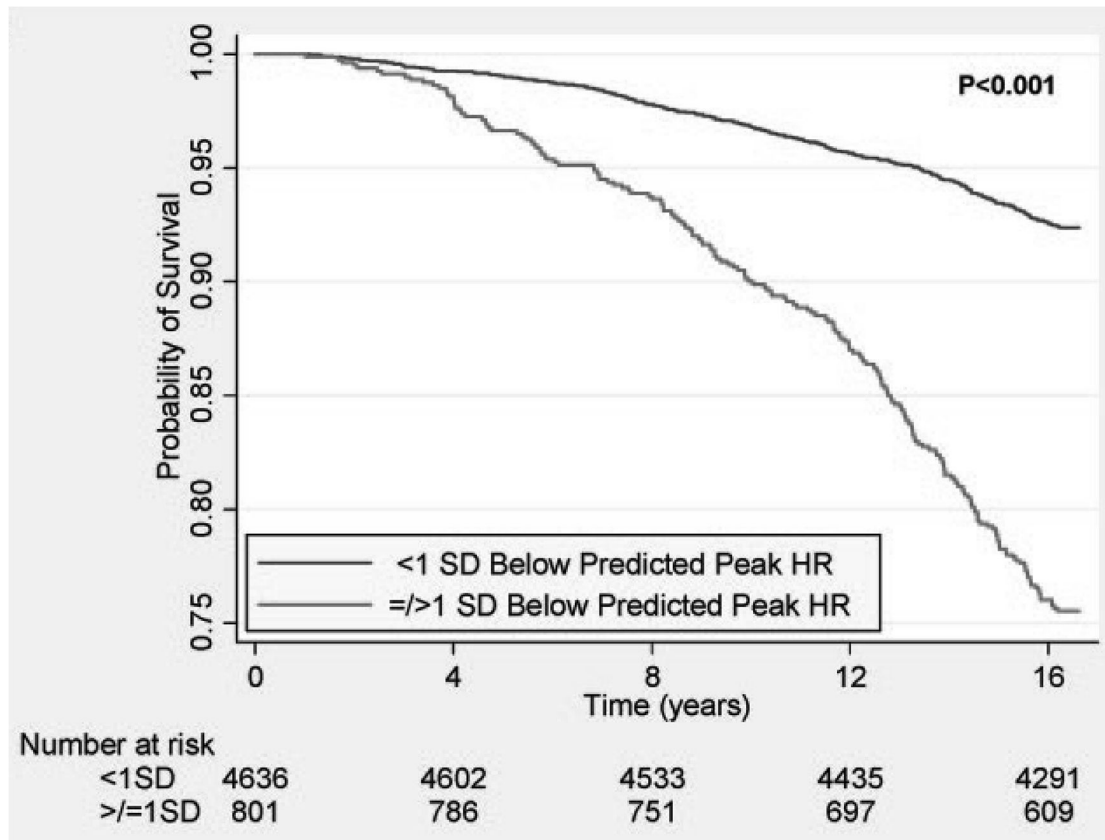


Figure 5. Markedly reduced survival during long-term follow-up among asymptomatic women with peak HR ≥ 1 SD below the average. From Gulati et al, *Circulation* 2010;122:130-137.

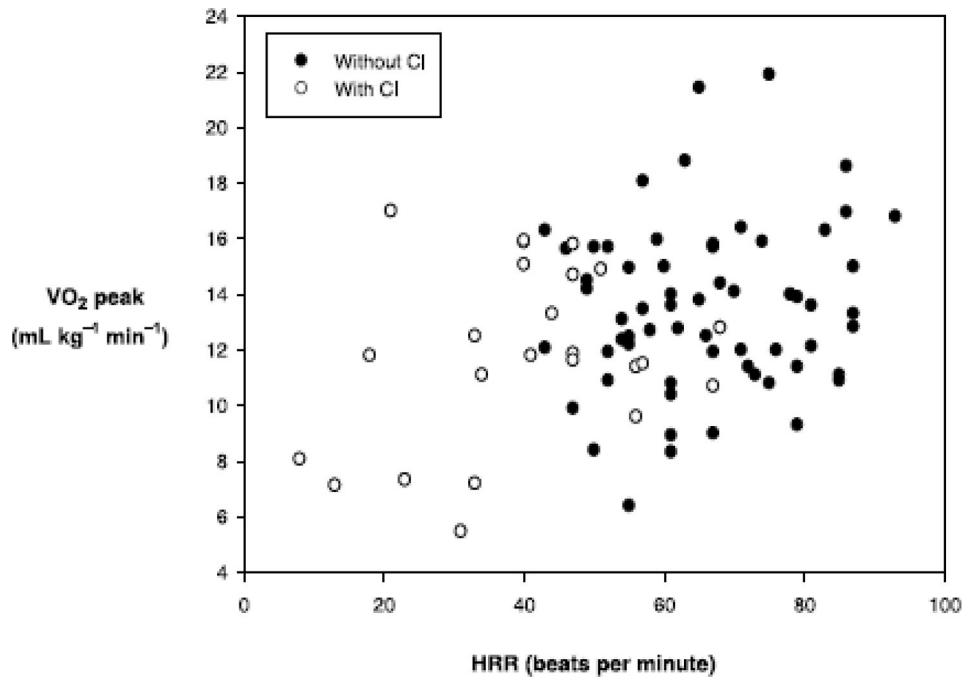


Figure 6. Relationship of heart rate reserve (HRR) to peak exercise oxygen consumption (VO₂ peak) in older patients with HFrEF and HFpEF with (open circles) and without (closed circles) CI. There is a significant correlation between HRR and VO₂ peak in those with (R=.39 p=0.04) and without CI (R=.41 p =0.01). From Brubaker, et al, Journal of Cardiopulmonary Rehabilitation 2006; 26:86-89.

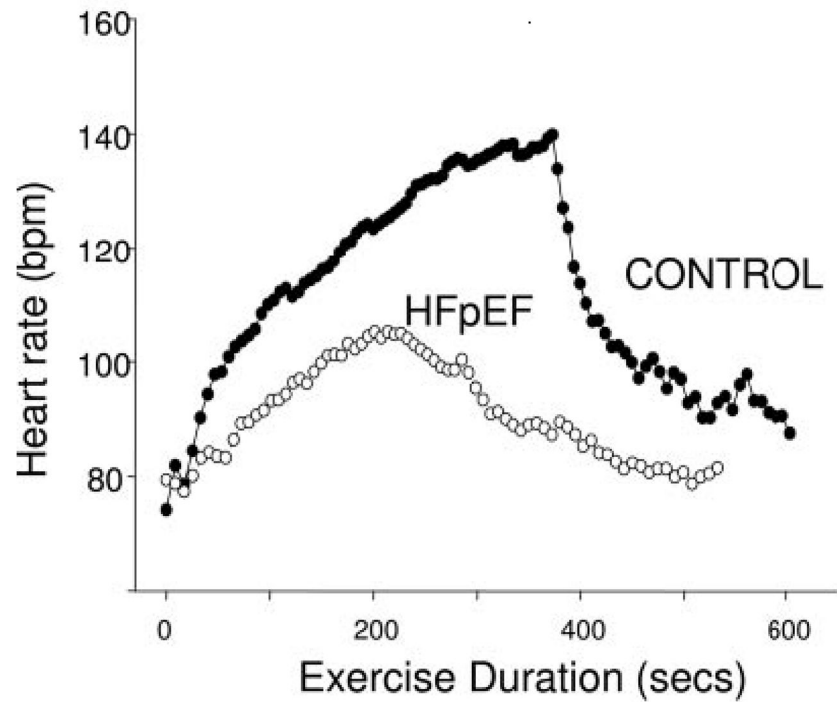


Figure 7. Heart rate profiles during and after cycle ergometry in patients with HFpEF compared to age and gender matched subjects who possessed similar co-morbidities to the HFpEF group including left ventricular hypertrophy (Control). These data demonstrate the delayed and attenuated heart rate response often seen in chronotropically impaired heart failure patients. From Borlaug et al, *Circulation* 2006; 114:2138-2147.