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 that impairs quality of life, and is an independent predictor of major adverse cardiovascular events and overall mortality. However, the importance of CI is underappreciated, and CI is often overlooked in clinical practice. This may be due in part to multiple definitions, the confounding effects of aging and 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 heart failure (HF). CI is common and can be diagnosed by objective, widely available, inexpensive methods; it 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 (V̇O₂). During maximal aerobic exercise in healthy humans, V̇O₂ increases approximately 4-fold. This is achieved by a 2.2-fold increase in heart rate (HR), a 0.3-fold increase in stroke volume, and a 1.5-fold increase in arteriovenous oxygen 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 of or a significant contributor to severe, symptomatic exercise intolerance.

**HR Control**

HR 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 the sinoatrial node is approximately 100 beats per minute (bpm), resting HR in humans is generally much lower (60 to 80 bpm) owing to the predominant 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 bpm has been associated with increased mortality in patients with stable coronary artery disease and left ventricular (LV) dysfunction.

An intact HR response is vital for tight matching of a subject’s cardiac output to 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 HF.

Immediately after the termination of exertion, sympathetic withdrawal and increased parasympathetic tone to the sinoatrial 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 adjustment for severity of cardiovascular disease, LV function, and exercise capacity. Although there are a number of methods available to evaluate 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 bpm (or <18 bpm if recovery was “active,” eg, unloaded cycling or slow walking) or a decrease in HR from peak exercise to 2 minutes of recovery of <42 bpm.

In contrast, highly trained athletes often display a rapid and profound drop in HR of ≥30 to 50 beats during the first minute of recovery from strenuous exertion. The rate and magnitude of HR recovery after exertion appear to be directly related to the level of parasympathetic tone. The association between early HR recovery and parasympathetic nervous system function was elegantly demonstrated in a study of 3 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 nonlinear 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).
imbalance of sympathetic and parasympathetic activity, observed after cessation of exercise. In conclusion, the autonomic responses at rest and both during and after exercise, is strongly associated with increased risk of adverse cardiovascular outcomes and sudden death.9

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 HR in response to exercise that is inexorable, highly predictable, and occurs in other mammalian species as well as humans.3,15,16 The age-related decline in maximal HR is the most substantial age-related change in cardiac function, both in magnitude and consequence.3,15,18 It is primarily responsible for the age-related decline in peak aerobic exercise capacity.3,18 Starting from early adulthood, maximal HR declines with age at a rate of approximately 0.7 bpm per year in healthy sedentary, recreationally active, and endurance-exercise-trained adults.19 Although the mechanisms are not fully understood, dual-blockade studies show that intrinsic HR declines by 5 to 6 bpm for each decade of age such that resting HR in an 80-year-old is not much slower than the intrinsic HR.15 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.15 There are also significant alterations in the sympathetic influence on HR response to exercise with aging, with increased circulating catecholamines and reduced responsiveness.15 Doses of isoproterenol that increase HR by 25 bpm in healthy young men produce an increase of only 10 bpm in older persons.15

The normal age-related decline in maximal HR during exercise is not significantly modified by vigorous exercise training, which suggests that it is not due to the age-related decline in physical activity level.15 Also, it does not appear to be due to inadequate sympathetic stimulation, because both serum norepinephrine and epinephrine are increased rather than decreased at rest in healthy elderly persons. Furthermore, 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 bpm−age) was developed on the basis of studies primarily conducted in middle-aged men, some of whom had known coronary artery disease and were taking β-blockers.19,20 This equation has been associated with tremendous intersubject variability, with a standard deviation of ±11 bpm21 that increases to ±40 bpm in patients with coronary heart disease who are taking β-blockers.22 Consequently, an alternative formula from Tanaka et al (208−0.7×age) is gaining acceptance for determination of age-predicted maximal HR (APMHR), even though it may still underpredict APMHR in older adults (Figure 2).21

Several earlier studies suggested that gender affected the HR trajectory during exercise and recovery and that the traditional equation (220−age) overestimated maximal HR in younger women but underestimated it in older women.19,21 A meta-analysis indicated that maximal HR was unaffected by gender.21 A recent large prospective study in >5000 asymptomatic women showed that the traditional equation significantly overestimated maximal HR and thus proposed a new equation in which maximal HR = 206−0.88×age.19 Brawner et al22 demonstrated that the 220−age equation is not valid in patients with coronary heart disease taking β-adrenergic blockade therapy and developed the equation 164−0.7×[time] age for this population.

All of the aforementioned studies improve on estimations of maximal HR versus the traditional 220−age approach but still produce substantial standard deviation of the estimate (10 to 22 bpm). Given the inherent variability in maximal HR, regression equations that use 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 estimation of predicted maximal HR, we suggest the selection of an equation that was generated in a population that most closely matches the population of interest. In this regard, the equation suggested by Tanaka et al.\(^2\) is recommended for apparently healthy persons, and the equation of Brawner et al.\(^2\) is recommended for those with known or suspected cardiovascular disease. Although 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% to 89%) in the literature.\(^3\) In an evaluation of >1500 CI patients referred for pacemaker implantation, the use of 5 different definitions of CI resulted in a prevalence of CI of 34% to 87%.\(^2\) CI has been most commonly diagnosed when HR fails to reach an arbitrary percentage (either 85%, 80%, or less commonly, 70%) of the APMHR (usually based on the 220–age equation described above) obtained during an incremental dynamic exercise test.\(^2\)–\(^3\) 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. Because 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 (percent) HR reserve, determined from the change in HR from rest to peak exercise divided by the difference of the resting HR and the APMHR, commonly has been used.\(^3\) The majority of studies in the literature have used failure to attain ≥80% of the HR reserve, measured during a graded exercise test, as the primary criterion for CI.

However, before one concludes that a patient has CI, it is important to consider the patient’s level of effort and reasons for terminating the exercise test. Patients should be encouraged to continue on the exercise modality until true symptom-limited (exhaustive) maximal levels are achieved. Symptoms and subjective ratings of perceived exertion can provide an estimate of exertion level and are an acceptable method. The respiratory exchange ratio (RER; ie, volume of carbon dioxide produced divided by volume of oxygen consumed) obtained from expired respiratory gas analysis at peak exertion during the exercise test is the most definitive and objective clinically available measure of physiological level of effort during exercise. RER is reliable, and although its measurement 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, which should lead to caution in diagnosing CI.

Wilkoff et al.\(^3\) used the expired gas analysis technique to more objectively evaluate CI using the relationship between HR and \(\dot{V}_{O_2}\) 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 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 physiological concept allows for a single HR achieved at any point during an exercise study (HRstage) to be determined as consistent or inconsistent with normal chronotropic function. This is accomplished by use of the following formula, in which metabolic equivalents (METS) = \(\dot{V}_{O_2}\) (in mL·kg\(^{-1}\)·min\(^{-1}\))/3.5:

\[
\text{Estimated HR}_{\text{stage}} = \frac{[(220–\text{age} – \text{HR}_{\text{rest}})]}{[(\text{METs}_{\text{stage}} – 1)/ (\text{METs}_{\text{peak}} – 1)] + \text{HR}_{\text{rest}}}
\]

The Wilkoff model predicts the MCR slope of the normal sinus response to be 1.0, with a 95% confidence interval between 0.8 and 1.3.\(^3\) An MCR slope or any single MCR value (from 1 stage) ≤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 the following: Age; resting HR (HR\(_{\text{rest}}\)); APMHR (defined as 220–age); age-predicted HR reserve (APHRR), defined as APMHR–HR\(_{\text{rest}}\); observed maximal HR during exercise test (HR\(_{\text{max}}\)); oxygen consumption (\(\dot{V}_{O_2}\) in mL·kg\(^{-1}\)·min\(^{-1}\)) at each stage and at peak effort; and RER. For example, in a 60-year-old subject who only achieved an RER of 0.96 at peak exertion (ie, submaximal effort), the following data from a submaximal stage (25 W) of exercise (HR\(_{\text{rest}}\) 67 bpm; HR\(_{\text{peak}}\) 100 bpm; HR\(_{\text{rest}}\) 97 bpm, METS\(_{\text{25W}}\) 3.3, METS\(_{\text{peak}}\) 3.7) when entered into the Wilkoff equation would result in a CI index of 0.66 (actual HR\(_{\text{stage}}\) of 97/estimated HR\(_{\text{stage}}\) of 147), which is well below the CI cutoff of ≤0.80. The Wilkoff approach\(^3\) can be combined with other methods to determine the presence of CI.
in challenging situations, such as the following: (1) If despite reaching a peak exercise RER >1.05 (which suggests adequate effort), the patient fails to achieve an HRmax ≥80% to 85% of APHRR (or 80% to 85% HR reserve), or (2) if RER does not reach 1.05 (which suggests submaximal effort), an MCR relationship of <0.80 can be used. Although a variety of exercise testing protocols (Bruce, RAMP, etc) and modes of testing can be used, a specific CI exercise testing protocol has been used in some laboratories that evaluates the MCR relationship from 2 stages on a treadmill protocol (stage 1=1.3 mph and 0.5% grade and stage 2=3.0 mph and 1.5% grade). The process of data collection and analysis described above is subsequently used to determine the adequacy of the chronotropic responses.32 Savonen et al33,34 have proposed methods that attempt to separate the effects of parasympathetic withdrawal versus sympathetic stimulation on the HR response to exercise. This is based on physiological observations that the HR increase below 100 bpm is predominantly controlled by gradual withdrawal of parasympathetic tone, whereas from 100 bpm 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% to 100% of maximal work capacity on the exercise test predicts mortality and acute myocardial infarction better than the peak HR or HR reserve approaches. Similarly, another study35 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. Although 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 β-blockers, digitalis, certain calcium channel blockers, amiodarone, and others, can confound the determination of CI.36,37 β-Blockers may result in pharmacologically induced CI and obscure identification of an underlying intrinsic abnormality in neural balance.37 In one study,38 a suitable threshold for CI among HF patients using β-blockers was found to be ≥62% of APHRR. With this lower HR threshold, CI could be identified reliably and was an independent predictor of death.38 These modified criteria have been used to design clinical trials.39 Care should be taken before these modified threshold criteria are applied to ensure that the patient is taking a nontrivial dose and is compliant with the medication.

The use of separate CI criteria for patients taking β-blocker medications has been challenged by other studies that failed to demonstrate any effect of β-blockers, including at a high dose, on the occurrence of CI.40 Figure 3 shows the similar relationship between HR reserve and V˙O2 peak in HF patients who were either taking or not taking β-blockers. Similarly, Jorde and colleagues41 examined the relationship between exercise time and HR during treadmill exercise testing in HF patients. As seen in Figure 4, the HR slope was abnormal in HF patients with CI, yet β-blockers had no impact on this relationship in these patients.42 Although still an evolving
concept, chronic treatment of HF patients with β-blockers may paradoxically improve chronotropic response by decreasing sympathetic tone or increasing β-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 after 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 CI and Mortality**

The relationship between CI and increased cardiac and all-cause mortality was first reported more than 30 years ago by Hinkle et al. They described a group of men who were unable to reach an expected HR on a standard exercise protocol and who subsequently experienced an increased frequency of cardiac events during 7-year follow-up. These investigators initially termed this inadequate HR response a “sustained relative bradycardia.” Subsequently, others described a relationship between this phenomenon and autonomic dysfunction. Ellestad et al. confirmed the finding of 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 >5000 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 defined a particularly high-risk group of patients with potential candidates for heightened treatment. The prognostic value of an impaired HR response to exercise appears to persist even after the adverse effects of coronary artery disease or LV dysfunction are considered.

In another study of 3221 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 adjustment for LV function and exercise-induced myocardial ischemia. Azarbal et al. showed that a low percentage of HR reserve was a superior predictor compared with an inability to achieve 85% of APMHR, because the latter 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 β-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 or 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 United States 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 ejection fraction (HFpEF). A hallmark characteristic of chronic HF, either HF with reduced ejection fraction (HFrEF) or HFpEF, is a markedly reduced capacity for physical exertion, with a subsequent reduction in VO2peak that is 15% to 40% below that of age-matched control subjects. Work from our group and others has shown that patients with HFpEF have similar reductions in exercise tolerance, measured as peak exercise oxygen consumption (VO2peak), and have similar reduced submaximal exercise measures, ventilatory anaerobic threshold, 6-minute walk distance, quality of life, and markers of prognosis, including VE/VCO2 slope, as those with HFrEF. These findings have been replicated by Smart et al. and others.

According to the Fick equation, an appropriate increase in VO2peak during exertion is dependent on both an increase in cardiac output and 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 with HF. In addition, patients with HF often achieve <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 VO2peak.
The reduced cardiac output response of HF is often attributed to an attenuated stroke volume, subsequent to either systolic or diastolic LV dysfunction. Stroke volume, already diminished at rest in the HF patient subsequent to systolic or diastolic abnormalities, rises only modestly to a peak of 50 to 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. Although maximal HR during exercise may be reduced only mildly at peak exertion, HR reserve (ie, degree of HR augmentation above resting levels) is often blunted more substantially in HF patients owing to the sympathetically driven elevation in resting HRs.

**Contribution of Impaired HR Response to Exercise Intolerance in HF**

As described previously, the Fick equation dictates that an increase in cardiac output during exertion is dependent on an increase in stroke volume, HR, or both. 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 the degree of effort. Yet, given the potential impact of HR responsiveness on cardiac output and subsequent VO$_2$peak, it is surprising there has not been more interest in CI in a patient population in which exercise intolerance is so problematic. We recently demonstrated that in a group of 102 elderly patients with either HFrEF or HFpEF, HR reserve (the difference between resting and peak HR achieved on a bicycle exercise test) was significantly correlated ($r=0.40$) with VO$_2$peak (Figure 6). Moreover, these findings indicated that the increase in HR during exercise accounted for an appreciable portion (ie, 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 mL·kg$^{-1}$·min$^{-1}$, abnormal HR accounts for approximately 2 mL·kg$^{-1}$·min$^{-1}$ ($±16\%$) and therefore has significant functional and prognostic ramifications.

Similarly, Witte et al$^{37}$ found, using <80% of either APMHR or HR reserve, that the average VO$_2$peak was significantly lower ($−2.6$ mL·kg$^{-1}$·min$^{-1}$, or 14%), and $−4.6$ mL·kg$^{-1}$·min$^{-1}$, or 25%, respectively) in HFrEF patients with CI than in those without CI. Furthermore, Witte et al$^{37}$ reported a correlation between VO$_2$peak and ΔHR (peak exercise HR−rest HR) of 0.56 and 0.60 for β-blocked and non–β-blocked HF patients, which further supports the significance and impact of an inadequate HR increase during exertion in this population.

Borlaug et al$^{69}$ evaluated parameters of exercise tolerance in HFrEF patients versus a control group without HF but matched on age, gender, important comorbidities, and LV hypertrophy (controls). At peak exertion, the HFrEF patients had significant reductions in VO$_2$peak (9.0±3.4 versus 14.4±3.4 mL·kg$^{-1}$·min$^{-1}$, respectively) and HR (87±20 versus 115±22 bpm, respectively) compared with controls. Exercise capacity, expressed as VO$_2$peak, correlated directly with cardiac output but was determined primarily by HR and afterload responses during exercise. In contrast, changes 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, which indicates abnormal autonomic function in these patients (Figure 7).$^{69}$

**Prevalence of CI in HF**

The reported prevalence of CI within the HF population has varied considerably, with a range of 25% to 70%. This substantial variability is likely influenced by the criteria used to determine CI, as well as differing patient characteristics (age, disease severity, type/dose of medications). In one of the earliest papers to evaluate the prevalence of CI in HF, Clark and Coates$^{70}$ using <80% of APMHR as the criterion, found that approximately 28% of stable, non–β-blocked systolic HFrEF patients (mean age 59 years) demonstrated CI. In contrast, Roche et al$^{71}$ using achievement of ≤80% of APCHRR as the predetermined criterion, determined that 14 (67%) of 21 stable, non–β-blocked HFrEF patients (mean age...
54±10 years) demonstrated CI. Furthermore, Roche et al found no significant difference in age, HR, peak oxygen uptake, or LV ejection fraction between patients with and without CI. In a slightly older group of HFrEF patients, Witte et al found that 103 (43%) of 237 HF patients met the criterion of <80% of APMHR, whereas 170 (72%) of 237 met the criterion of <80% of APHRR. Witte et al did indicate that patients taking β-blockers were more likely to have CI than those not taking β-blockers when <80% APMHR was used (49% versus 32%, respectively) or <80% APHRR was used (75% versus 64%, respectively). In contrast, when the criterion of <62% APHRR was used for HF patients taking β-blocker therapy, a significantly smaller percentage (22%) of patients were identified with CI.

We evaluated the prevalence of CI in older (≥60 years) HFrEF and HFrEF patients and in age-matched healthy subjects using ≤80% of APMHR and the Wilkoff approach. Although CI was uncommon in healthy older adults (just 2 of 28 subjects, or 7%), the prevalence of CI was relatively similar between older HFrEF (12 of 46, or 26%) and HFrEF (11 of 56, or 20%) patients. A more recent unpublished analysis of 207 older HFrEF patients tested in our laboratory indicated that 28% of these patients met the CI criteria as described previously. Phan et al also observed abnormal HR responses to exercise in HFrEF patients versus age-matched hypertensive and healthy control subjects. Using the criterion of <80% APMHR, Phan et al observed a similar prevalence of CI among HFrEF patients of 35%. As in other studies that used multiple criteria, the prevalence of CI increased to 63% of HFrEF patients when 80% of HR reserve was used 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 used) of both HFrEF and HFrEF populations also have significant CI that contributes 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 downregulation of β-receptors and desensitization in the presence of increased circulating catecholamine levels. Bristow and colleagues found a 50% or greater reduction in β-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 with normal in adenylyl cyclase elaboration and up to a 73% reduction in muscle contraction. These findings suggest that in HF patients, a decrease in β-receptor density leads to a diminished sensitivity of the β-adrenergic pathway and a decrease in β-agonist–stimulated muscle contractility.

Samejima et al demonstrated that the ratio of change in HR to change in log of norepinephrine (ΔHR/Δlog NE), an index of sinoatrial node sympathetic responsiveness, decreased progressively with the severity of HF. Furthermore, the ΔHR/Δlog NE ratio during exercise was significantly correlated with anaerobic threshold, VO2, and VE/VCO2 slope. An electrophysiology study of symptomatic HFREF patients and age-matched normal subjects undergoing radiofrequency ablation for atrioventricular tachycardia or atrioventricular nodal tachycardia demonstrated that compared with non-HF subjects, HF patients with no prior atrial arrhythmias have significant sinus node remodeling characterized by (1) anatomic 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 commonly seen 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 postexercise HRs. Most of these HR adaptations appear to be related to an alteration in the balance of the 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 neurohormonal activation in chronic HF include increased baroreflex sensitivity and HR variability and reduced sympathetic outflow and 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, which leads to autonomic derangement and neurohormonal activation. Moreover, Hasking et al found that plasma norepinephrine concentrations sampled during supine rest were increased in patients with asymptomatic LV dysfunction and increased 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 one third. Although 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 studies79–81 have demonstrated that peak exercise HR increases 5% to 7% and contributes to the increase in cardiac output and VO2peak usually observed in HF patients with exercise training. A meta-analysis of 35 randomized studies of exercise training in HF patients82 indicated that peak HR increased by an average of 4 bpm, or 2.5% of the pretraining level. Keteyian et al83 demonstrated that after 24 weeks of endurance exercise training, peak exercise HR increased by 7% (≈9 bpm) yet remained unchanged in a nonexercise control group. Furthermore, the training-induced increase in peak HR accounted for 50% of the increase in VO2peak (2 mL·kg−1 · min−1, or 14%) in the exercise training group. Although alterations in β-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 VO2 during exercise in a variety of patient populations, including HF,83 in which a 2- to 6-bpm increase in HR is associated with a 1-mL·kg−1 · min−1 increase in VO2 during exercise. Consequently, rate-adaptive pacing has been shown to enhance functional capacity in patients with an inadequate chronotropic response84 and those meeting formal definitions of CI.32,85 Despite the potential to improve HR, cardiac output, and subsequently VO2 during exertion in HF patients with chronotropic impairment, rate-adaptive pacing in this population has received minimal attention.86,87 Furthermore, it may be counterintuitive for some clinicians to believe certain HF patients may benefit from a pacemaker, particularly in the absence of bradycardic/heart block.

The potential benefit of rate-adaptive pacing, in conjunction with cardiac resynchronization therapy, for exercise performance in HFrEF patients was assessed by Tse et al.88 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 VO2. 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) DDRR 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 VO2peak. However, in the HF patients with more severe CI (those achieving <70% APMHR), rate adaptation significantly increased peak HR, exercise time, and VO2peak. Furthermore, in the majority (82%) of these patients, the improvement in chronotropic response with rate-adaptive pacing was associated with an ≈20% increase in VO2peak.

For the majority of patients with less severe CI (those achieving 70% to 85% of APMHR), there was little or no benefit, and one third of the patients experienced a reduction in exercise capacity with rate-adaptive pacing.88 Although it appears that rate-adaptive pacing has potential benefit in carefully selected patients with HFrEF, advances in this area are hindered by lack of standardized, accepted definitions, and selection criteria. Furthermore, at this time, it is unclear whether CI is causal or simply a marker of advanced disease and whether treating this with a pacemaker would improve functional status in HFrEF patients. Clearly, this issue requires further investigation.

Even less is known regarding pacing in patients with HFpEF. The current RESET trial (Restoration of Chronotropic Competence in Heart Failure Patients With Normal Ejection Fraction) is designed to evaluate the effect of rate-adaptive pacing in HFpEF patients with overt CI.39 The rationale for this intervention is based on observations that ≈30% of this population have CI and that impairment in chronotropic function contributes significantly to their objectively measured exercise intolerance.42,68,69 The outcome of this randomized controlled trial has the potential to help determine whether 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 one third 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 β-receptor density and sensitivity secondary to increased sympathetic drive.89

The diagnosis of CI should take into account the confounding effects of aging, physical condition, and medications but can be achieved objectively with the use of widely available exercise testing methods and standardized definitions. A 3-step approach to assessment is suggested. First, a progressive, exhaustive, symptom-limited exercise test should be performed. If practical, this should include automated expired gas analysis with a standard, commercially available system for assessment of RER, which objectively verifies level of effort, and peak VO2. Then, a formula for peak HR that is relevant to the patient’s profile should be applied. In general, this will be the Tanaka formula for apparently healthy persons21 and the Brawner formula for those with cardiovascular disease or taking β-blockers.22 If the patient fails to achieve 80% of APMHR on this test despite good/maximal effort (judged by rating of perceived exertion, 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, β-adrenergic blockade may have a less detrimental effect on exercise capacity than previously thought and may even paradoxically improve exercise performance. β-Blockers and other negative inotropes do not appear to have a major impact on HR response to exercise in HF patients, and thus, the use of separate CI criteria for these patients does not appear necessary. Furthermore, it appears that β-blockers may not increase the prevalence of CI in HF patients substantially. The potential of more novel β-blockers to reduce the prevalence of CI in HF patients is unclear. Although exercise training and rate-adaptive pacing have been shown to improve chronotropic responses and exercise capacity in HF, it is clear that 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 research.

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**References**

17. Deleted in proof.


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Chronotropic Incompetence: Causes, Consequences, and Management
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