Dialogues in Cardiovascular Medicine is a peer-reviewed, quarterly journal for cardiologists and physicians with an interest in cardiology. Its aim is to provide a comprehensive analysis of a single topic in cardiovascular medicine. Each issue consists of a single lead article, written by an international expert, which explores the topic in concise detail. Three pressing questions that dominate the field are identified and given personal replies by undisputed authorities in the Expert Answers section. The Summaries of Ten Seminal Papers put the topic into historical perspective. The Fascinomata Cardiologica section takes a thought-provoking and at times unconventional approach to cardiology from a variety of vantage points. Finally, a selected Bibliography of One Hundred Key Papers is available for those readers who wish to undertake a more exhaustive investigation of the topic. Dialogues offers unique coverage of the state of the art in clinical cardiology. The journal is indexed in medical databases and is part of the continuing medical education programs of several major international cardiological societies.
Chronotropic Incompetence

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In the past decade, cardiology has experienced a reappraisal of the importance of increased heart rate as a prognostic indicator, and in some circumstances, such as heart failure (HF) and coronary artery disease (CAD), as a risk factor that requires specific treatment.

This interest was triggered by: (i) the discovery of $I_f$ channels in sinus node cells capable of determining and controlling heart rate; and (ii) the consequent development of ivabradine, a sinus node inhibitor, able to selectively reduce heart rate without any other major hemodynamic effects.

There is no doubt that we still have a great deal to learn about heart rate because the important clinical benefits obtained with ivabradine both in HF and CAD need a pathophysiological explanation. Studies related to the effects of heart rate on endothelial sheer stress and the progression of atherosclerosis are under way as are studies on the relationship between heart rate and inflammation, apoptosis, and/or hypertrophy.

We are certain that the interest in heart rate will not be a “one-off” event. This is confirmed by this issue of *Dialogues in Cardiovascular Medicine*, which is dedicated to chronotropic incompetence (CI) as a way to investigate the behavior of heart rate, not
in a “static” way at rest, but in a “dynamic” way during and after exercise. Most of these heart rate adaptations appear to be related to an alteration in the balance of sympathetic and parasympathetic influences of the autonomic nervous system, which in turn modulates the If channels. Such a dynamic heart rate response that accompanies our daily life is a highly complex phenomenon. An increase in heart rate is the largest contributor to the ability to perform exercise; thus, failure to achieve maximal heart rate, inadequate submaximal heart rate, and heart rate instability during exercise are all indications of an impaired chronotropic response. This, in turn, is a common manifestation of aging (with a relative reduced capacity to perform exercise) and of HF and CAD, which are all conditions in which quality of life can be severely reduced. The rate of heart rate recovery is also important as it reflects the integrity of the parasympathetic nervous system. A delayed heart rate recovery after exercise is associated with increased all-cause mortality in both asymptomatic and diseased populations. It follows that we need a “dynamic” approach to heart rate because resting heart rate and heart rate during exercise and recovery are closely related to each other and to prognosis.

In rather simplified terms, the so called “heart rate reserve” is the difference between resting and peak heart rate; therefore, reduction in resting heart rate will increase the reserve and diminish CI. This reduction can be obtained with heart rate–reducing agents such as β-blockers, some Ca²⁺ blockers, and ivabradine.

Maximal heart rate during exercise, but not resting heart rate, declines with age and explains the physiologically reduced physical activity in elderly patients, a phenomenon most likely related to reduced parasympathetic tone at rest as well as altered sympathetic influence on heart rate response during exercise.

In view of the importance of CI in our daily life and our future, the obvious questions are: (i) what is the best method to assess CI; (ii) what are the causes of an impaired response; and (iii) what is the best pharmacological and nonpharmacological treatment?

These questions will be addressed in this issue of Dialogues. The lead article by Dalane W. Kitzman discusses the importance of understanding HR profile changes before, during, and after exercise, how these changes relate both to physical performance and to disease prognosis, and effective ways to manage and treat impaired HR responses. In the subsequent articles, three key questions regarding CI in patients with cardiovascular disease will be addressed by experts in the field. First, Alain Cohen-Solal and Florence Beauvais will discuss the role of heart rate response in the diagnosis and measurement of CI. Second, Damien Cullington, Imran Sunderji, John G. F. Cleland, Klaus K. Witte, and Andrew L. Clark will examine the clinical consequences of CI in
chronic heart failure patients and how β-blocker therapy affects the patient’s outcome. Finally, Marco Metra will look at CI as a potential therapeutic target to improve the prognosis of patients with cardiovascular disease.

There are more than just superficial resemblances between “chronotropic incompetence” and the “Peter Principle,” a corollary to which states: “Work is accomplished by those employees who have not yet reached their level of incompetence”—add “cardiac” before “work,” replace “employees” by “heart,” and add “chronotropic” before “incompetence” and the Peter Principle can easily make it into MEDLINE. Just as the “Peter Principle” turned out becoming one of the major shibboleths of (business) management in the early 70s, the nearly contemporary appearance of the concept of “chronotropic incompetence” is likewise proving to be increasingly rich in implications in terms of (cardiac) management, and this is what medicine is all about: from observation to theory to treatment.
Chronotropic incompetence: causes, implications, and management

Dalane W. Kitzman, MD

Department of Internal Medicine (Cardiology) - Wake Forest School of Medicine - Winston-Salem - North Carolina - USA

The important role of heart rate (HR) in cardiovascular disease is well established, but attention to HR is usually limited to discussion of resting HR or HR at peak exercise. This article discusses the importance of evaluating HR profiles during and after exercise. Increasing HR to tightly match cardiac output with metabolic demand during exercise is critical to physical performance. The increase in HR during exercise is the greatest contributor to the ability to perform physical work, an important determinant of quality of life, and a strong predictor of prognosis. The high prevalence of impaired exercise HR response and its easy assessment in clinical practice provides the rationale for routine screening for inadequate HR response, particularly because this condition is potentially treatable and its management can lead to significant improvements in exercise tolerance and quality of life.

It is likely that heart rate (HR) responsiveness (chronotropy) was the first aspect of dynamic cardiac function to be observed. HR response is easily measured by a variety of techniques during physiological stressors. As a result, it is often assumed that chronotropy in health and disease is “settled science”; all that need be known regarding it is already established, its role in clinical practice is fully matured, and related research questions are nonexistent. Indeed, it has been learned that HR responsiveness is a critical aspect of cardiac health, strongly predictive of outcomes, readily assessable, leads to improved patient outcomes, and that modification of chronotropic abnormalities can be achieved by a variety of therapeutic techniques.

However, dynamic HR responsivity is a highly complex phenomenon, and the medical science related to it is an area of active investigation since disorders of chronotropy are relatively common. This overview will highlight what is known, and what remains to be learned, regarding the important topic of chronotropy.

RESTING HR CONTROL

Instantaneous HR reflects the dynamic balance between the sympathetic and parasympathetic divisions of the autonomic nervous system. Although the intrinsic rate of depolarization of the sinoatrial node is 100 bpm, resting HR in humans is generally much lower (60 to 80 bpm).

This is likely due to the dominant influence of parasympathetic efferents (vagus nerve). Increased resting HR levels, due to increased sympathetic and/or decreased parasympathetic influence, are associated with increased cardiovascular death, ischemic heart disease, and sudden cardiac death in asymptomatic men and women, as well as in patients with known coronary artery disease and left ventricular (LV) dysfunction.
ABNORMAL STIMULATED HR RESPONSE AND ITS CONTRIBUTION 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 persons, VO$_2$ increases approximately 4-fold. This is achieved by a 2.2-fold increase in HR, a 0.3-fold increase in stroke volume, and a 1.5-fold increase in arteriovenous oxygen (A-VO$_2$) difference. The increase in HR is the largest contributor to the ability to perform sustained aerobic exercise. Therefore, an abnormal HR response to exercise can be the primary cause of, or a significant contributor to, severe, symptomatic exercise intolerance. In turn, exercise intolerance is a common manifestation of aging and a variety of specific disorders, including coronary artery disease and heart failure, and is also associated with a reduced quality of life.

Thus, an intact HR response is critical for tightly matching a subject’s cardiac output to metabolic demands during exertion. Failure to achieve maximal HR, inadequate submaximal HR, or HR instability during exertion are examples of impaired chronotropic response. These types of abnormal chronotropy are relatively common in patients with sick sinus syndrome, atrioventricular block, coronary artery disease, and especially heart failure (HF), and can occur in the absence of structural heart disease. As discussed below, chronotropic abnormalities are also independent predictors of adverse clinical events.

HR RECOVERY

Immediately after the termination of exertion, sympathetic withdrawal and increased parasympathetic tone to the sinoatrial node combine to cause a rapid decline in HR. Highly trained athletes often display a much larger drop in HR than sedentary subjects.

The role of the parasympathetic nervous system in early HR recovery was shown in a study of athletes and normal subjects where 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. The initial steep decrease in HR was abolished when the subjects were given atropine and exercise testing was repeated.

A delayed recovery of HR after exertion is independently associated with increased all-cause mortality in a variety of asymptomatic and diseased populations. The Framingham Offspring study and MRFIT (Multiple Risk Factor Intervention Trial) demonstrated that a delayed HR recovery is an independent predictor of all-cause death in asymptomatic persons. While there are a number of thresholds used to indicate abnormal HR recovery, the most widely used, and which is associated with increased risk of all-cause mortality, is a decrease in HR from peak exercise to 1 minute of passive supine recovery of <12 bpm (or <18 bpm if recovery was “active,” such as unloaded cycling or slow walking) and/or a decrease in HR from peak exercise to 2 minutes of recovery of <42 bpm. Cahalin et al recently reported that HR recovery can be assessed, even if a maximal exercise end point was not achieved, if expired gas analysis is used to measure and account for the level of effort.

RELATIONSHIP BETWEEN HR DURING REST, STRESS, AND RECOVERY

HR at rest, during exercise, and during recovery are intimately related to each other and to prognosis. Since HR reserve (HRR) is the difference between resting and peak HR, increased resting HR can reduce HRR and contribute to abnormalities of stimulated chronotropy. In a long-term, 23-year follow-up study of asymptomatic...
working men who underwent exercise stress testing, 23 factors independently associated with increased risk of fatal myocardial infarction, were a resting HR more than 75 bpm, an increase in HR from rest to peak exercise less than 89 bpm, and a decrease in HR less than 25 bpm after the cessation of exercise. The interrelatedness of these 3 components of HR control was also shown in an intervention study. Jolly et al showed that exercise training improved HR recovery in a group of over 1000 patients with cardiovascular disease undergoing phase 2 cardiac rehabilitation. 24 Patients with abnormal HRR at baseline who normalized HR recovery with exercise training had a mortality similar to that of individuals with baseline normal HR recovery. Thus, 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. 18

**EFFECT OF AGE AND SEX ON MAXIMAL HR RESPONSE TO EXERCISE**

Resting HR is unchanged with adult aging. However, in healthy men and women, there is a marked age-related decrease in maximal HR in response to exercise that is inexorable and predictable and occurs in other mammalian species as well as humans. 7,25,26 The age-related decline in maximal HR is the most substantial biological age-related change in cardiac function, both in magnitude and consequence. 7,27,28 It is primarily responsible for the age-related decline in aerobic exercise capacity. 7,28 From early adulthood, maximal HR declines with age at a rate of ≈0.7 bpm/year in healthy sedentary, recreationally active, and endurance exercise-trained adults. 19 Although the mechanism(s) of this decline 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. 25 This indicates that there is reduced and minimal parasympathetic tone at rest. This is supported by the fact that the increase in HR after atropine in an older person is less than half that in the young. 27 There are also significant alterations in the sympathetic influence on HR response to exercise in aging, with increased circulating catecholamines and reduced responsiveness. 27 Doses of isoproterenol that increase HR by 25 bpm in young healthy men produce an increase of only 10 bpm in older persons. 27 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. 25 It also does not appear to be due to inadequate sympathetic stimulation, since 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 normal maximal HR (220 bpm – age), was developed based on studies primarily in middle-aged men, some of whom had known coronary artery disease and were taking β-blockers. 29,30 This equation has large intersubject variability with a standard deviation of ±11 bpm that increases to ±40 bpm in patients with coronary heart disease receiving β-blockers. 32 An alternative formula from Tanaka et al (208 – 0.7 × age) is becoming more accepted for determining age-predicted maximal HR (APMHR) even though it may still underpredict APMHR in older adults (Figure 1). 31
Earlier studies suggested that sex affected the HR trajectory during exercise and recovery, and that the traditional equation (220–age) overestimates maximal HR in younger women, but underestimates in older women. A meta-analysis indicated that maximal HR was unaffected by sex. A prospective study in over 5000 asymptomatic women showed that the traditional equation significantly overestimates maximal HR and thus proposed a new equation where maximal HR = 206 – 0.88 × age. Also, Brawner et al demonstrated that the 220–age equation is not valid in patients with coronary heart disease taking β-adrenergic blockade therapy and subsequently developed the 164 – 0.7 × age equation for this population.

Given the inherent variability in maximal HR, regression equations using a single predictor variable, such as age, are unlikely to be 100% accurate. However, efforts to improve on the estimations of maximal HR beyond the traditional 220–age approach, generally by increasing the number of predictor variables, still produce substantial error of estimates (10 to 22 bpm) and reduce practicality for clinical use. Thus, it is suggested that for estimating predicted maximal HR, an equation should be selected that was generated in a population that most closely matches the target population. 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. These are practical and generally superior to the traditional equation that only accounts for age.

DEFINITION, CRITERIA, AND MEASUREMENT OF CHRONOTROPIC INCOMPETENCE

Chronotropic incompetence (CI) is most commonly diagnosed when HR fails to reach an arbitrary percentage (either 85%, 80%, or less commonly, 70%) of the APMHR 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, termed the heart rate reserve (HRR). Since the proportion of HR achieved during exercise depends in part on resting HR, the chronotropic response to exercise can also be assessed as the fraction of HR achieved at maximal effort. Thus, adjusted HRR, determined from the HRR divided by the difference between the resting HR and the APMHR, has been commonly used. For simplicity, the majority of studies have used “failure to obtain ≥80% of the HRR obtained during a graded exercise test” as the primary criteria for CI.

It is important to consider the level of effort and reasons for terminating the exercise test before diagnosing CI. Patients should be encouraged to continue exercising until a true symptom-limited (exhaustive) maximal level is achieved. Symptoms and subjective ratings of perceived exertion (RPE) can provide an estimate of exertion level. However, respiratory exchange ratio (RER, ie, 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, reliable, and clinically available measure of physiologic level of effort during exercise. RER is a continuous variable, ranging from <0.85 at quiet rest to >1.20 during intense, exhaustive exercise. Higher RER values increase confidence that maximal effort was achieved. RER <1.05 at peak exercise suggests submaximal effort and should lead to caution in diagnosing CI.

A number of alternative approaches to assessment of CI have been described, including ones that are more detailed, physiological, efficient, and practical. Wilkoff et al utilized expired gas analysis to evaluate CI more objectively using the relationship between HR and oxygen consumption (VO₂) during exercise. With this approach, the metabolic-chronotropic relationship (MCR) is calculated from the ratio of the HRR 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 HRR achieved during exercise equals the percentage of metabolic reserve achieved. This concept allows determination of whether a single HR achieved at any point during an exercise study is consistent with normal chronotropic function. The Wilkoff approach can be combined with other methods to determine the presence of CI in challenging situations: (i) if despite reaching a peak exercise RER of greater than 1.05 (suggesting adequate effort), the patients fail to achieve a maximal HR ≥80% - 85% of age-predicted heart rate reserve (APHR) or (80% - 85% of HRR); and (ii) if RER does not reach 1.05 (suggesting submaximal effort) an MCR relationship of <0.80 can be used as indicative of CI.

In testing for CI, a variety of standard protocols (such as Bruce, ramp, and others) and a variety of modes of testing (bicycle ergometer, treadmill) can be utilized. A CI exercise testing protocol has been employed in some laboratories and evaluates the MCR relationship from 2 stages on a treadmill protocol. This technique has merit since it is relatively specific to CI, could be
standardized, and is more efficient; however, it has not been widely utilized. Although a formal maximal exercise test is usually recommended, it is resource intensive and burdensome to patients. Girotra et al recently showed, using a large, US, population-based, observational study of persons aged $\geq$65 years (Cardiovascular Health Study), that the HR response to a timed walk test is predictive of future events.38 This highlights the powerful prognostic ability of chronotropic response. This innovative approach merits further investigation to determine its diagnostic ability in a broad range of individual patients. This practical approach could provide a badly needed, simple, and quick screening tool that could significantly expand assessment for CI in routine clinical practice. Patients who appear to have abnormalities on the quick screening tool could then be referred for formal CI testing.

**EFFECT OF MEDICATIONS AND OTHER CONFOUNTHING INFLUENCES ON CI**

Many common cardiovascular medications, including $\beta$-blockers, digitalis, 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 $\leq$62% of APHRR.16 Using this lower HR threshold, CI was able to be reliably identified and was an independent predictor of death.16 Care should be taken before applying these criteria to ensure that the patient is on a nontrivial 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 any effect of $\beta$-blockers, including at high dose, on the occurrence of CI.39 Figure 2 shows the similar relationship between HRR and peak exercise oxygen consumption (peak VO$_2$) 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.40 As seen in Figure 3 (page 144), the HR slope was abnormal in HF patients with CI, yet $\beta$-blockers had no impact on this relationship in these patients.41 Recently, Dobre et al showed in the large HF-ACTION trial (Heart Failure: A Controlled Trial Investigating Outcomes of exercise traiNing) population that chronotropic index was predictive of events in HF patients even when there was a very high rate of $\beta$-blocker usage.42 Interestingly, chronic treatment of HF patients with $\beta$-blockers may paradoxically improve chronotropic response by decreasing sympathetic tone and/or by increasing $\beta$-receptor activity.10 This would agree with the recent mechanistic findings of Benes et al,43 and may provide a clue that could be systematically exploit-

![Figure 2. Relationship between change in HR during exercise (ΔHR) and peak VO$_2$ in patients with HFREF.](image-url)
ed in future intervention studies for CI. Furthermore, there may be potentially important differences between β-blockers in the relationship between HR reduction and exercise capacity.44 Future studies of CI in patients on β-blockers could take advantage of methods proposed by Savonen et al14,45 attempting to partition the effects of parasympathetic withdrawal versus sympathetic stimulation on the HR response to exercise. This is based on the physiological observations that the HR increase below 100 bpm is predominantly controlled by a gradual withdrawal of parasympathetic tone, whereas from 100 bpm to maximum the HR increase is predominantly the result of increasing sympathetic nervous system activity.

Criteria for diagnosis of CI in the presence of atrial fibrillation have not been established. Exercise testing can be used to assess adequacy of response following pacemaker insertion for CI by reprogramming or suspending the device with a magnet, taking care to ensure the patient is not completely pacemaker-dependent beforehand.

**CONTRIBUTION OF IMPAIRED HR RESPONSE TO EXERCISE INTOLERANCE IN HF**

A hallmark of chronic HF is a markedly reduced capacity for physical exertion, with a subsequent 15% to 40% reduction in peak VO₂ compared with healthy, matched controls.46 We have shown that patients with HF and preserved ejection fraction (HFREF) have similar reductions in peak VO₂, exercise time, ventilatory anaerobic threshold, and 6-minute walk distance as patients with HF and severely reduced ejection fraction (HFREF).47

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**Figure 3. Heart rate vs exercise time in CI.**
In patients with HF, β-blockers do not significantly impact the relationship between HR and exercise time, regardless of whether CI is present.

**Figure 4. Comparison at seated rest, 12W, 25W, and peak exercise between HFPEF patients and normal controls.**
Determinants of peak exercise oxygen consumption (peak VO₂) in older patients with HFPEF (closed circles) compared with healthy age-matched normal controls (open circles). HR is reduced at peak exercise and is the main contributor to reduced peak cardiac output, which accounts for about 50% of the reduction in peak VO₂ compared with controls. Thus, HR response is reduced in older HFPEF patients and contributes to their exercise intolerance. All variables adjusted for sex (*P<0.05).

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Reduced peak VO₂ in HFREF as well as HFPEF is due to a combination of reduced peak cardiac output and A-VO₂ difference. The latter is related to abnormalities of skeletal muscle and vascular function that limit exercise intolerance associated with HF. The reduced cardiac output response in HF patients is variable due to reduced stroke volume and HR during peak exercise. We recently showed that the impaired HR response in elderly patients with HFPEF is the main determinant of their reduced exercise cardiac output, accounts for about 50% of the reduced peak VO₂ compared with normal matched controls (Figure 4), and is a stronger contributor to reduced peak VO₂ than stroke volume. Whereas maximal HR during exercise may be only mildly reduced, HRR is often blunted more substantially in HF patients due to the sympathetically driven increase in resting HR.

We recently demonstrated in elderly patients with HF, both HFREF or HFPEF, that HRR was significantly correlated (r=0.40) with peak VO₂ (Figure 5). Furthermore, the increase in HR during exercise accounted for an appreciable portion (15%) of the observed differences in peak VO₂. This was unchanged even after accounting for medications, including β-blockers. These findings were confirmed and expanded by Borlaug et al who reported that HFPEF patients also had a slower HR rise and impaired HR recovery, indicating abnormal autonomic function.

**PREVALENCE OF CHRONOTROPIC INCOMPETENCE IN HEART FAILURE**

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 employed to determine CI as well as by differing patient characteristics. In older HFREF patients, Witte et al found that 103 out of 237 (43%) HF patients met the criterion of <80% of APMHR, whereas 170 out of 237 (72%) met the criterion of <80% of APHRR. Patients taking β-blockers were more likely to have CI than those not taking β-blockers when <80% of APMHR was used (49% vs 32%, respectively) or <80% APHRR was used (75% vs 64%, respectively). When the criteria of ≤62% APHRR is used for HF patients on β-blocker therapy, a significantly smaller percentage (22%) of patients were identified with CI.

We evaluated the prevalence of CI in older (≥60 years) patients with HFREF and HFPEF as well as in age-matched healthy subjects using ≤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 out of 46 [26%]) and HFPEF (11 out of 56 [19%]) patients. Phan et al reported that the prevalence of CI increased to 63% of HFPEF patients when a criterion of 80% of HRR was employed as the definition of CI. Thus, a significant portion (one-third or more depending on criterion employed) of both HFREF and HFPEF patients have significant CI contributing to their exercise intolerance.

**MECHANISMS OF CHRONOTROPIC INCOMPETENCE IN HF**

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 more 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 adenylate cyclase elaboration and up to 73% reduction in muscle contraction. These find-
ings suggest that in HF patients, a decrease in β-receptor density leads to a diminished sensitivity of the β-adrenergic pathway and decrease in β-agonist–stimulated muscle contractility. Samejima et al demonstrated that the ratio of change in HR 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 peak, and VE/VCO2 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 with non-HF subjects, HF patients with no atrial arrhythmias have significant sinus node remodeling, characterized by: (i) anatomical and structural changes along the crista terminalis; (ii) prolonged sinus node recovery and sinoatrial conduction; and (iii) caudal localization of the sinus node complex with circuitous propagation of the sinus impulse. This reduction in sinus node reserve appears to be a potential contributor to the bradycardia, and possibly the CI, commonly seen in HF.

A recent study expanded upon these findings. Benes et al compared the prognostic impact and biomarker correlates of both resting HR and CI in 81 patients with advanced, yet stable, well-characterized HFREF and compared these with 25 age-, sex-, and size-matched healthy controls. Their report underscores the high prevalence of CI in the HF population. Two-thirds of the HF patients met formal criteria for CI, a proportion that is substantially higher than the 25% that we observed in older HFREF patients, but is within the wide range (20% to 70%) reported in the HF literature. A novel aspect of the investigation by Benes et al was the use of biomarker/neurohormonal profiling. This technique rests on the well-grounded assumption that elaboration of individual biomarkers and neurohormones are triggered by a variety of specific conditions, and that they can be grouped in clusters according to their clinical and mechanistic inferences, including increased myocardial stress, inflammation, myocyte injury, and neuroendocrine response to HF. Benes et al partitioned the components of CI (resting HR and HRR). Surprisingly, the resting HR and HRR were not intercorrelated and were associated with distinct biomarker profiles, suggesting that these 2 measures may have different mechanisms/pathophysiology. Resting HR correlated with myocardial stress and inflammation, while HRR correlated with neurohormonal activation. Interestingly, in healthy controls, the HRR was highly correlated with increase in plasma norepinephrine, but this relationship was uncoupled in HF patients, suggesting diminished sinus node responsiveness in the latter group. This finding is consistent with other lines of evidence, including that from Samejima et al discussed above.

**CHRONOTROPIC INCOMPETENCE AND PROGNOSIS**

Over 40 years ago, Hinkle et al were the first to report on the relationship between CI and increased cardiac and all-cause mortality. They described a group of men who were unable to reach the expected HR on a standard exercise protocol and who subsequently experienced increased frequency of cardiac events during a 7-year follow-up. They initially termed this inadequate HR response “sustained relative bradycardia.” Creager et al and Eckberg et al subsequently described a relationship between this phenomenon and autonomic dysfunction. Ellestad et al confirmed the finding of an 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. They suggested the term “chronotropic incompetence” to describe the phenomenon of abnormal HR response during exercise.

A number of subsequent studies expanded on these findings, reporting that an attenuated HR response to exercise was predictive of increased risk for mortality and acute coronary events, independent of a variety of other confounding factors, including age, sex, physical fitness, traditional cardiovascular risk factors, and ST-segment changes during exercise. A combination of CI and a myocardial perfusion defect during exercise stress testing carried a particularly high risk, thus identifying a 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 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 adjusting for LV function and exercise-induced myocardial ischemia. Azarbal et al showed that a low HRR% was a superior predictor compared with an inability to achieve 85% of APMHR, as the former 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. In HF patients not taking β-blockers, the presence of CI appears to increase mortality risk. Furthermore, as discussed earlier, Dobrev et al recently showed in the large HF-ACTION trial population that reduction in chronotropic index was predictive of events in HF patients even when there is a very high rate of β-blocker usage. In a recent report, Benes et al examined the prognostic impact of resting HR and HRR, both independently and combined in a small group of well-characterized patients with advanced HFREF. Over a mean follow-up of 469 days, 28 patients (34.6%) experienced an adverse event. Patients with a low resting HR (≤67 bpm) had a lower risk of adverse outcomes compared with those in the upper quartile of resting HR. In contrast, patients in the lowest quartile of HRR (≤0.38) had an increased risk of adverse outcomes. Furthermore, the combined quartile analysis of resting HR and HRR provided incremental prognostic information with the highest risk (hazard ratio, 7.95; 95% CI, 2.01–53; P=0.002) if both parameters were abnormal. Thus a high resting HR combined with a low HRR portended the worst prognosis for advanced HFREF.

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.

**MANAGEMENT OF CHRONOTROPIC INCOMPETENCE: 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 HR, as well as a more rapid decline in postexercise HR. Most of these HR adaptations appear to be related to alteration in the balance of sympathetic and parasympathetic influence of the autonomic nervous system.

Endurance exercise training generally improves exercise tolerance in HF patients as well as through a variety of potential central and peripheral mechanisms. The effects of exercise training on autonomic dysfunction and neurohormonal activation in chronic HF include increased baroreflex sensitivity and HR variability, and reduced sympathetic outflow, plasma levels of catecholamines, angiotensin II, vasopressin, and brain natriuretic peptides at rest. While the mechanisms of these changes have not been clarified, exercise training modifies the abnormal afferent stimuli from the failing heart that tend to increase sympathetic outflow, leading to autonomic derangement and neurohumoral activation.

Several exercise training studies have demonstrated that peak exercise HR increases 5% to 7% and contributes to the increase in cardiac output and peak VO₂ usually observed in HF patients with exercise training. A meta-analysis of 35 randomized studies of exercise training in HFREF patients indicated that peak HR increased by 4 bpm or 2.5% of the pretraining level. Keteyian et al demonstrated that after 24 weeks of endurance exercise training, peak exercise HR increased by 7% (approximately 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 peak VO₂ in the exercise-training group. While alterations in β-adrenergic receptor sensitivity may explain these findings, the mechanisms responsible for the improved chronotropic response with exercise training in HFREF are not known. We recently reported that exercise training in HFPEF patients improves peak HR (Figure 6, page 148), but this was counterbalanced by reduced stroke volume response, such that cardiac output did not change with exercise training. Thus, in HFPEF improved CI may not contribute to improved exercise capacity due to exercise training, which appears primarily due to improved peripheral mechanisms. However, more information is needed regarding the impact of exercise training on the chronotropic response in HFREF and HFPEF patients.

**MANAGEMENT OF CHRONOTROPIC INCOMPETENCE: RATE-ADAPTIVE PACING**

During exercise, there is a linear relationship between HR and VO₂ in a variety of populations, including HF. Rate-adaptive pacing has been clearly shown to enhance functional capacity in a variety of patients with CI. However, despite the prominent role of abnormal HR responses and the frequency of formal CI in HF, there has been relatively modest attention to rate-adap-
tive pacing in this specific population. This may be due in part to the fact that it is unclear whether CI in HF is causal or simply a marker of advanced disease and if treating this with a pacemaker will improve functional status and clinical outcomes (events) in HFREF patients.

Tse et al examined the potential benefit of rate-adaptive pacing, in conjunction with cardiac resynchronization therapy, on exercise performance in HFREF patients. Twenty HFREF patients with CI with an implanted cardiac resynchronization device underwent exercise testing with measurement of VO$_2$. In the overall group, rate-adaptive pacing during cardiac resynchronization therapy increased peak exercise HR and exercise time, but did not increase peak exercise VO$_2$. However, in the 11 HF patients (55%) with more severe CI (those achieving <70% APMHR), rate adaptation significantly increased peak HR, exercise time, and peak VO$_2$. Further, in the majority of these patients (82%), the improvement in chronotropic response was associated with a 20% increase in peak VO$_2$. However, in patients with less severe CI there was little or no benefit, and one-third of the patients had a reduction in exercise capacity with rate-adaptive pacing. In the ADEPT trial (ADVanced Elements of Pacing randomized controlled Trial), which did not specifically focus on HF, there was little benefit from rate-adaptive pacing. In long-term follow-up of a randomized trial, rate-adaptive pacing in patients with HFREF appeared to be potentially detrimental to LV function and increased clinical events. Thus, while it appears that rate-adaptive pacing may have potential benefit in carefully selected patients with HFREF, further work is needed, and standardization of definitions, selection criteria, timing, and mode will be important.

Even less is known regarding the impact of pacing on HFPEF, despite the fact that up to 30% of HFPEF patients have CI, that impaired chronotropic response is a contributor to their objectively measured severe exercise intolerance, and that they also appear to have abnormal HR recovery. One trial was designed to help determine if rate-responsive pacing can potentially improve exercise performance function in HFPEF patients with overt CI. A recent report of a pilot study in a small group of HFPEF patients, who did not necessarily have CI, but had atrial dyssynchrony, indicated that left atrial pacing with a goal of restoring atrial synchrony led to a beneficial increase in 6-minute walk distance.

A recent report noted that CI is common in clinical HF patients who already have implanted pacemakers and is associated with worse exercise capacity. Furthermore, the authors recommended periodic optimization of pacemaker settings and reevaluation of β-blocker dosages.
SUMMARY

CI is common, an important cause of exercise intolerance and reduced quality of life, and is an independent predictor of major adverse cardiovascular events and mortality. It occurs in a number of disorders, is present in up to one-third of patients with HF, and contributes to their prominent exertional symptoms. 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 3-step approach to assessment is suggested. Firstly, to conduct a progressive, symptom-limited exercise test that optimally should include expired gas analysis and be available with commercially available systems, in order to assess RER and objectively verify level of effort and peak VO₂. Secondly, to utilize a formula for peak HR that is relevant to the patient’s profile: the Tanaka formula for apparently healthy persons and the Brawner formula for those with cardiovascular disease or on β-blockers. If the patient fails to achieve 80% of their APMHR despite good/maximal effort (judged by RPE, symptoms, and RER levels), then the Wilkoff Chronotropic Index should be calculated. Thirdly, to search for potentially reversible causes if CI is found to be present. In HF, β-adrenergic blockade may have less detrimental effect on exercise capacity than previously thought, and may even paradoxically improve exercise performance. The potential of more novel β-blockers to reduce the prevalence of CI in HF patients is unclear. While exercise training and rate-adaptive pacing improve chronotropic responses and exercise capacity in HF, more research is needed to fully evaluate the impact of these therapies on key clinical outcomes.

CI is common, easily diagnosed, and potentially treatable; it should be considered by clinicians whenever they encounter patients with symptoms of exertional intolerance.

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Chronotropic Incompetence

Expert Answers to Three Key Questions

1. What are the criteria of chronotropic incompetence in patients with cardiovascular disease and how is it measured?
   
   A. Cohen-Solal, F. Beauvais

2. What are the clinical consequences of chronotropic incompetence in patients with cardiovascular disease?
   
   D. Cullington, I. Sunderji, J. G. F. Cleland, K. K. Witte, A. L. Clark

3. What are the therapeutic implications of chronotropic incompetence in patients with cardiovascular disease?
   
   M. Metra
What are the criteria of chronotropic incompetence in patients with cardiovascular disease and how is it measured?

Alain Cohen-Solal, MD, PhD, FESC¹,²,³; Florence Beauvais, MD³

¹UMR-S 942
²Université Paris 7 - Denis Diderot
³Cardiologie - Hôpital Lariboisière - Assistance Publique Hôpitaux de Paris - Paris - FRANCE

Heart rate response plays a major role in the cardiac response to exercise. Chronotropic incompetence (CI)—the inability of the heart to mount a rate response appropriate to demand—impairs quality of life in heart disease, in particular when stroke volume response is limited, as in heart failure or coronary artery disease. The diagnosis of CI presupposes a consensus as to the definition of a “normal” maximal heart rate response: although this has long been recognized as essentially age-related, the classic Astrand rule of thumb (220 beats/min less the patient’s age in years) has attracted criticism on the grounds of intersubject variability and has prompted numerous counterproposals. None are valid across the board, but some are clearly superior and readily applicable in specific patient subpopulations.

Selected Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>AMPHR</td>
<td>age-maximal predicted heart rate</td>
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<tr>
<td>APHRR</td>
<td>age-predicted heart rate reserve</td>
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<tr>
<td>bpm</td>
<td>beats per minute</td>
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<td>CAD</td>
<td>coronary artery disease</td>
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<tr>
<td>CI</td>
<td>chronotropic incompetence</td>
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<tr>
<td>HF</td>
<td>heart failure</td>
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<tr>
<td>HF-ACTION</td>
<td>Heart Failure: A Controlled Trial Investigating Outcomes of exercise training</td>
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<tr>
<td>HR</td>
<td>heart rate</td>
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<tr>
<td>ICD</td>
<td>implantable cardioverter-defibrillator</td>
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<tr>
<td>MECR</td>
<td>metabolic/chronotropic relationship</td>
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<tr>
<td>MIBG</td>
<td>metaiodobenzylguanidine</td>
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<tr>
<td>MVO₂</td>
<td>myocardial oxygen consumption</td>
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<tr>
<td>RER</td>
<td>respiratory exchange ratio (exhaled CO₂/inhaled O₂)</td>
</tr>
<tr>
<td>SEE</td>
<td>standard error of the estimate</td>
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Heart rate (HR) plays a major role in the cardiac response to exercise. During exercise, oxygen consumption can rise from 250 mL/min at rest to a peak exceeding 5000 mL/min in athletes, with a concomitant increase in cardiac output from 5 L/min to 30 L/min. Given that the increase in stroke volume seldom exceeds 50% from its resting value, it is clear that the increase in HR plays a major role in adaptation to exercise. It is thus not surprising that cardiologists have long tried to define and quantify the optimal HR response to exercise and characterize its abnormalities.

The quality of HR response is important not only for maximal exercise in athletes, but also for the activities of daily living that require continuous adjustment by the heart to varying output demand and changes in preload and afterload. In patients with cardiovascular disease, given the limitations on stroke volume in conditions such as heart failure (HF) or coronary artery disease (CAD), the
role of HR response is even more important, since it bears the brunt of the burden in adjusting to exercise.

A final consideration is that while an abnormal HR response is pathologic, a normal HR response may in some circumstances have paradoxically deleterious effects. In CAD, increased HR may promote ischemia by increasing myocardial oxygen consumption (MVO₂) and increasing perfusion time. Similarly, in HF, excessive HR can be deleterious due to a negative force-frequency relationship (the higher the HR, the lower the increase in contractility). 1 In patients with delayed or slowed cardiac relaxation, excessive HR may impair cardiac output response by restricting diastolic filling.

**THE NORMAL HEART RATE RESPONSE TO EXERCISE**

During exercise, HR increases regularly in response to increasing metabolic demand until it reaches a maximum. Whether the slope of increasing oxygen consumption (VO₂) begins to flatten out at the end of exercise or near peak remains debated. The established determinants of increasing HR are a decrease in vagal tone at the beginning of exercise, followed by an increase in sympathetic tone.

**Normal resting heart rate**

Resting HR depends on the relative balance between sympathetic and parasympathetic tone, and ranges from 25 to 30 beats per minute (bpm) in competitive cyclists to over 100 bpm in patients with severe HF. Between these extremes, resting HR averages 65 to 80 bpm, depending on fitness, blood volume, temperature, and stress.

**Normal maximal heart rate**

Although there is no age-related change in resting HR in healthy humans, there is a marked and inexorable age-related decrease in maximal HR in response to exercise. What constitutes a normal age-maximal predicted HR (AMPHR) in a maximal graded test on a bicycle ergometer or treadmill is a matter of much debate. The value decreases with age. Table I shows a selection of the many equations used. The most classic is that of Astrand et al: 220–age, giving a maximal HR of about 150 bpm in a 70-year-old subject and 200 bpm in a 20-year-old subject. The equation was derived from a study conducted in few subjects and has shown tremendous intersubject variability, with a standard deviation of ±11 bpm. 3,4 It has thus attracted considerable criticism (see some counterformulae in Figure 1 and Table I).

A meta-analysis has shown that sex does not affect maximal HR 4 However, the Astrand equation overestimates maximal HR in younger women while underestimating it in older women. 4–6 A prospective study in >5000 asymptomatic women showed that the equation significantly overestimated maximal HR and thus proposed a new equation: 206 – 0.88 × age. 6 The equation is also imprecise (SD ± 40 bpm) in CAD patients taking β-blockers, prompting a further new equation for such patients. 3 Other parameters affecting the equation include the type of exercise (treadmill or cycle) and the difficulty of the protocol (slow
versus rapid increase in load): it is usually more difficult to achieve AMPHR in a protocol with a rapidly increasing work rate.

All the above adjustments to the original Astrand equation are improvements, but still subject to substantial standard deviation. Given the inherent variability in maximal HR, regression equations that use a single predictor variable, such as age, are unlikely to be 100% accurate. Increasing the number of predictor variables yields little improvement and reduces clinical practicality. Brubacker and Kitzman suggest selecting an equation for estimating predicted maximal HR that was generated in a population that most closely matches the population of interest. For example, the equation suggested by Tanaka et al. (Figure 2) is recommended for apparently healthy persons and that of Brawner et al. for those with known or suspected cardiovascular disease. Although still imperfect, these are superior to the conventional 220–age equation, while remaining practical. None of these equations are, of course, applicable in atrial fibrillation or other pathologic situations, such as sinus node disease or atrioventricular conduction block.

**METHODS OF DETERMINING THE NORMALITY OF HEART RATE RESPONSE**

A major limitation in the attempts to understand normal and abnormal HR responses to exercise is the lack of consistent methods for determining chronotropic incompetence (CI). Hence the wide range in the reported prevalence of CI (between 10% and 90%). Two basic indicators have been used for assessing chronotropic response and thus defining CI: (i) percentage of AMPHR achieved during the test; and (ii) percentage of normal predicted chronotropic response, based on resting HR in addition to AMPHR.

CI has been most commonly defined as a level of HR that fails to reach an arbitrary percentage (either 85%, 80%, or, less commonly, 70%) of the AMPHR usually based on the 220–age equation obtained during an incremental dynamic exercise test. CI has also been determined by HR response, defined as the change between resting HR and peak exercise HR during an exercise test. Because the proportion of actual HR achieved during exercise depends, in part, on the resting HR, the chronotropic response to exercise can also be assessed as the fraction of HR achieved at peak exercise. Thus, the adjusted (percent) HR reserve, determined from the change in HR from rest to peak exercise divided by the difference between resting HR and AMPHR, has commonly been used. Most studies have used failure to achieve 80% of HR reserve, measured during a graded exercise test, as the primary criterion for CI. Thus, a 60-year-old patient with a resting HR of 70 bpm would need to reach a HR of 142 bpm to be chronotropically competent. However, many conditions need to be considered before diagnosing CI. It is important to consider the patient’s level of exertion and the reasons for terminating the exercise test. Patients should be encouraged to exercise to exhaustion. Symptoms and subjective ratings of perceived exertion can provide an estimate of the exertion level and are an acceptable method. Achieving > 18 on the Borg scale of exhaustion (maximum 20) is also accepted as valid. The respiratory exchange ratio (RER: VCO₂/O₂) obtained from expired respiratory gas analysis at peak exercise is the most definitive and clinically objective measure of physiologic effort.
A value <1.05 suggests submaximal effort or premature termination of the test, which should prompt caution in diagnosing CI.

A useful approach, proposed by Wilkoff and Miller, is to correlate HR response to work rate (WR) or the oxygen uptake (VO₂) response, with HR response being expressed as the slope of HR to WR and of HR to VO₂. The metabolic-chronotropic relationship (MCR), or chronotropic index, is then calculated from the ratio of HR reserve to metabolic reserve during submaximal exercise. The advantage of this method is that it adjusts for age, physical fitness, and functional capacity, while appearing unaffected by the exercise test 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 test (HRstage) to be deemed consistent or inconsistent with normal chronotropic function. This is accomplished using the following formula:

\[
\text{Estimated HRstage} = \left[\frac{220 - \text{age} - \text{HRrest}}{(\text{VO2stage})} \right] \times \left[\frac{(\text{VO2peak})}{\text{HRrest}}\right]
\]

The 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. An MCR slope or any single MCR value (from 1 stage) <0.80 is considered indicative of CI. Consequently, the information to be recorded for each patient during an exercise test to evaluate CI includes the following: age; resting HR (HRrest); AMPRH (220 bpm–patient’s age in years); age-predicted HR reserve (APHR), defined as AMPRH–HRrest; observed maximal HR during exercise (HRmax); and oxygen consumption (VO₂, in mL/min/kg) at each stage and at peak exercise. The Wilkoff approach can be combined with other methods to diagnose CI in challenging situations, such as those of a doubtful maximal exercise test. However, this method is not routinely used.

Although a variety of exercise test protocols (Bruce, ramp, etc) and modes can be used, some laboratories use a specific 2-stage treadmill protocol to evaluate MCR (stage 1: 1.3 mph and 0.5% grade, stage 2: 3.0 mph and 1.5% grade). They then use the above data collection and analysis procedure to determine the adequacy of the chronotropic responses.

**SPECIAL SITUATIONS**

Sinus node dysfunction inevitably reduces HR response. Mobitz type I block or Luciani-Wenckebach periodicity occurring during exercise also reduces maximal HR. 2/1 block is sometimes found in paced patients in whom an excessive HR is best avoided, eg, if they have exertional angina, or in those with an implantable cardioverter-defibrillator (ICD) and wide QRS complexes in whom the ICD may confuse the combination of a high HR and wide QRS complexes with ventricular tachycardia, resulting in inappropriate shock.

CI is the rule after transplantation, at least for the first few years, due to cardiac denervation causing an increase in HRrest (generally between 100 and 110 bpm) and an increase in the HR response to exercise that is both delayed and reduced. CI generally improves with time. In transplanted patients it is not possible to set the training level of a rehabilitation program from the HR response.

Drugs also affect HR response: digoxin, antiarrhythmics, verapamil, and diltiazem all reduce HR response, mainly by reducing HRrest. β-Blockers always reduce HR response, although to a degree that cannot always be predicted from the reduction in HRrest. Much depends on the type of β-blocker: non β1-selective blockers, β-blockers with intrinsic sympathomimetic activity (pindolol, acebutolol), or β-blockers with additional vasodilatory activities (celiprolol, nebivolol), which have less effect on HR response than the others. Ivabradine, a novel pure HR-reducing agent that selectively blocks the If channel in the sinus node, also affects HR response. It lowers HRrest, but also peak exercise HR due to a use-dependent phenomenon: the bradycardic properties of the drug increase when HR increases. However, in patients with CAD, exertional ischemia, and angina, ivabradine lowered the HR response to exercise slightly less than atenolol. Ivabradine also improved chronotropic reserve in stable angina patients when combined with low-dose bisoprolol compared with a double dose of bisoprolol.

A more frequent everyday situation is the evaluation of exercise capacity and HR response in HF patients receiving β-blockers. CI is common in such patients and may be compounded by β-blockade. In HF patients, early work by Colucci and Bristow showed that a decrease in cardiac β-receptor density leads to decreased sensitivity of the β-adrenergic pathway and decreased β-agonist-stimulated muscle contractility. Cardiac metaiodobenzylguanidine (MIBG) uptake (a more objective measure of cardiac denervation than plasma norepinephrine levels) showed a negative correlation between HR response and cardiac denervation in patients with moderate CHF (Figure 3). The question may thus be asked whether previous equations, derived mainly from normal subjects or those with
CAD, may apply to HF patients treated with β-blockers. Moreover, β-blocker doses in HF patients are often lower than in CAD patients because of poorer hemodynamic tolerance. Some of these patients are managed on a cocktail of β-blocker, ivabradine, digoxin, and amiodarone.

A new equation developed by Keteyian et al in HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of exercise training) in CHF patients with a low left ventricular ejection fraction may better predict maximum HR in these patients: $17 \text{AMPHR} = 119 + 0.5 (H R_{\text{rest}}) - 0.5 \times \text{age} - 0.5 (0, \text{if test was completed using a treadmill}; 5, \text{if using a stationary bike}).$ Validation of this equation yielded a mean $R^2$ and standard error of the estimate (SEE) of 0.28 and 18 bpm, respectively. For the classic 220–age equation, $R^2$ was –2.93, and SEE 43 bpm. Fernandes Silva et al found a significant relationship between age and maximal HR in 75 ischemic HF patients treated with β-blockers only with the following equation: $HR_{\text{max}} = 168 - 0.76 \times \text{age} (R^2 = 0.095; P = 0.007).$ They found no significant relationship in β-blocked patients with HF of nonischemic origin. Whether there is a correlation between CI and limited exercise capacity is unclear (Figure 4).19,20

**Figure 3. Relationship between heart rate response during a graded bicycle exercise and cardiac sympathetic denervation.**

This was assessed by the cardiac metaiodobenzylguanidine (MIBG) heart/mediastinum (H/M) ratio in 93 heart rate patients with left ventricular ejection fraction <35%. Despite the small sample, the figure suggests that lower peak heart rate is, at least in part, associated with decreased presynaptic reuptake of norepinephrine in these patients. Unpublished data from reference 16.

**Figure 4. Two cardiopulmonary exercise tests conducted 2 weeks apart in the same heart failure patient with low (2.5 mg/day) and high (10 mg/day) doses of bisoprolol.**

Despite clear chronotropic incompetence with the high dose (although resting heart rate was higher), peak VO₂ did not differ between the two tests. Hence, the need for caution in ascribing impaired physical capacity to chronotropic incompetence, especially in heart failure patients.

**Abbreviations:** EV, expiratory volume; HR, heart rate; VCO₂, carbon dioxide output; VO₂, oxygen consumption.
It is tempting, and possibly mistaken, to simply correlate exertional symptoms with CI. β-Blockers, for example, may affect exercise capacity and produce exertional fatigue by mechanisms other than CI, such as central effects and/or an altered relationship between lipids and carbohydrates as substrates for exercise muscle metabolism. Only the demonstration of improved exercise performance following CI correction can unequivocally demonstrate a cause-to-effect relationship. 21,22

A specific symptomatic aspect of CI may be related not to overall HR response throughout exercise, but to a blunted response only at the beginning of exercise, such as oppressive dyspnea in the first few minutes that decrease as exercise continues. Gas exchange may help also by showing an abnormal response at the beginning of exercise: during this period, a sudden increase in cardiac volume due to an increase in venous return, associated not with an increase in HR, but with a parallel increase in cardiac output, may result in a sudden increase in measured ventilation (Figure 5), often felt by the patient, and probably resulting from increased pulmonary pressures. The demonstration, on the contrary, of a decreased oxygen pulse response with exercise may also suggest a negative impact of excessive HR response on cardiac filling. Hence, the value of gas exchange analysis during graded testing in suggesting a deleterious role of CI or exercise HR.

**CONCLUSIONS**

HR response is a major determinant and component of the exercise response. An impaired response is usually associated with reduced exercise capacity and/or symptoms, especially in severely ill patients. Response is age-dependent and many studies have sought to quantify the expected normal predicted HR response to exercise. Drugs may also affect CI. Comprehensive cardiopulmonary exercise testing is often useful in confidently relating CI and exercise incompetence.

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What are the clinical consequences of chronotropic incompetence in patients with cardiovascular disease?

Damien Callington, MD, MRCP; Imran Sunderji, BSc, MBBS, MRCP; John G. F. Cleland, MD, FRCP; Klaus K. Witte, MD, FRCP; Andrew L. Clark, MA, MD, FRCP

Leeds Teaching Hospitals NHS Trust - Yorkshire Heart Centre - Leeds General Infirmary (DC, KKW); Hull and East Yorkshire Hospitals NHS Trust, Castle Hill Hospital, Kingston-Upon-Hull (IS, IGFC, ALC) - UNITED KINGDOM

This paper highlights 6 points: (i) chronic heart failure (CHF) patients have a high prevalence of chronotropic incompetence (CI), which varies depending on the definition of CI; (ii) there is no strong relation between chronotropic response to exercise and exercise capacity in CHF patients; (iii) CHF patients who take a β-blocker (vs not) have a higher prevalence of CI; (iv) in the long term, chronic β-blocker therapy is associated with better exercise tolerance. Stopping a β-blocker in a patient with CI does not improve exercise capacity; (v) there is no association between taking a β-blocker, dosing of β-blocker, and reduction in exercise capacity; and (vi) in patients with CHF, CI is not an independent prognostic marker of survival.

Selected Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CHF</td>
<td>chronic heart failure</td>
</tr>
<tr>
<td>CI</td>
<td>chronotropic incompetence</td>
</tr>
<tr>
<td>CIx</td>
<td>chronotropic index</td>
</tr>
<tr>
<td>HF-ACTION</td>
<td>Heart Failure: A Controlled Trial Investigating Outcomes of exercise training</td>
</tr>
<tr>
<td>HRR</td>
<td>heart rate reserve</td>
</tr>
<tr>
<td>LVEF</td>
<td>left ventricular ejection fraction</td>
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<tr>
<td>LVSD</td>
<td>left ventricular systolic dysfunction</td>
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<tr>
<td>MAPHR</td>
<td>maximum age-predicted heart rate</td>
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<tr>
<td>MPS</td>
<td>myocardial perfusion single-photon emission computed tomography</td>
</tr>
<tr>
<td>PEGASUS CRT</td>
<td>Pacing Evaluation-Atrial Support Study in Cardiac Resynchronization Therapy</td>
</tr>
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</table>

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HEART RATE RESPONSE TO EXERCISE IN HEALTH

Cardiac output is the product of stroke volume and heart rate. At rest, cardiac output is approximately 5 liters per minute, but can increase fourfold during heavy exertion. An increase in cardiac output during exercise is essential to maintain delivery of oxygen and energy substrates to the muscles, to remove the products of aerobic and anaerobic respiration, and to increase oxygen uptake from the lungs. An increase in heart rate is a major physiological response to exercise, but the mechanisms governing heart rate are complex.2,6 At rest, the normal heart rate is controlled by tonic parasympathetic outflow. At the onset of exercise, parasympathetic withdrawal results in an increase in heart rate. Increased venous return to the heart leads to an increase in cardiac output. The exercising muscle transmits neural signals centrally in response to exercise (via mechanoreceptors and the ergoreceptors), vasodilation in the vascular beds of the exercising muscle causes a fall in arterial blood pressure and consequent stimulation of the arterial baroreceptors. The inputs are integrated in brainstem centers, resulting in increased sympathetic stimulation of the heart and an increase in heart rate.

EXERTIONAL LIMITATION IN PATIENTS WITH CHF

For patients with CHF, exercise intolerance means exertional breathlessness—a very subjective descriptor. A variety of measures are used to try to standardize the level of symptom impairment, from the simple New York Heart Association (NYHA) classification, the 6-minute walk test, and ultimately, data derived from cardiopulmonary exercise testing (CPET).7 CPET is the “gold standard” test of exercise responses, as a result of its reproducibility and close relationship with prognosis, but it is not freely available since it requires moderately expensive equipment and specialist expertise to perform and to interpret the results.8,9

A purely hemodynamic understanding of exercise limitation in patients with CHF suggests that left ventricular (LV) impairment is a major determinant of exercise capability.10 However, we now know that severity of LV systolic dysfunction, at least at rest, correlates poorly with exercise capacity, and there are often multiple noncardiac contributors to exercise limitation.3,11-15 Patients with CHF have an impaired ability to increase their stroke volume during exercise and an increase in heart rate would seem logical as the main means by which cardiac output could then increase.16 As a result, it is widely thought that patients with CHF should have a greater heart rate response to exercise than normal subjects. The failure of heart rate to increase appropriately (ie, CI) may, therefore, be an important cause of limitation of exercise capacity.

THE ETIOLOGY OF CHRONOTROPIC INCOMPETENCE

One of the earliest compensatory changes in heart failure is sympathetic overactivity. Chronically, this results in adaptive cardiac β-adrenergic receptor downregulation, attenuated responsiveness to β-adrenergic stimuli, and sinus node dysfunction.17-19 As a result of these changes, the component of heart rate response to exercise driven by β-adrenergic stimulation is dampened, translating into what we measure as CI.20,21

### Table 1. Definitions of chronotropic incompetence (CI) and the normal heart rate response to exercise.

**Abbreviations:** CI, chronotropic incompetence; CIx, chronotropic index; HRR, heart rate reserve; MAPHR, maximum age predicted heart rate; RHR, resting heart rate.

<table>
<thead>
<tr>
<th>Basic definitions</th>
<th>Threshold value</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>% MAPHR&lt;sup&gt;1&lt;/sup&gt;</td>
<td>&lt;80% of MAPHR</td>
<td>Inability to increase heart rate to at least 80% of MAPHR during exercise eg, for 75-year-olds, 80% MAPHR = 116 bpm</td>
</tr>
<tr>
<td>% HRR</td>
<td>&lt;80% of HRR</td>
<td>([Heart rate at peak exercise – RHR] ÷ [MAPHR – RHR]) ×100 = %HRR eg, (130 – 70)/(145 – 70)×100 = 80%</td>
</tr>
<tr>
<td>CI&lt;sup&gt;2&lt;/sup&gt;</td>
<td>≤0.8</td>
<td>Proportion of HRR used at peak exercise: (Heart rate at peak exercise – RHR) ÷ (220 – age – RHR) = CIx eg, (130 – 70)/(220 – 75 – 70) = 0.8</td>
</tr>
</tbody>
</table>

### Note

1. MAPHR: Maximum age predicted heart rate (210 – age) <br>2. CI: Chronotropic incompetence
CHRONOTROPIC INCOMPETENCE—WHAT AND WHERE?

The three commonest definitions relating to the description of CI and the normal heart rate response to exercise are shown in Table 1.22,23 (page 165). These are described in more detail in the first article of the present series. The chronotropic index, devised by Wilkoff et al, is arguably better than other measures since it adjusts for age, fitness, and functional capacity, and can also be useful to assess the chronotropic response in patients undergoing submaximal exercise tests.22 The various definitions used to define CI make it impossible to accurately determine its prevalence.22-25 All calculations are based upon subjects without CHF and do not account for medications that lower heart rate.24

As severity of heart failure worsens, exercise capacity decreases and prevalence of CI increases. Jorde et al found that in a group of 278 pa-

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients with CHF (n)</th>
<th>Age (years)</th>
<th>SR (%)</th>
<th>LVSD</th>
<th>CI criteria</th>
<th>CI present (%)</th>
<th>FU (years)</th>
<th>BB treatment CI vs no CI (%)</th>
<th>pVO₂ CI vs no CI (mL/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al Najjar et al,28</td>
<td>411</td>
<td>66</td>
<td>81</td>
<td>83%</td>
<td>&lt;80% APHR</td>
<td>CI group I: 42.3</td>
<td>7.4</td>
<td>74 vs 60 (P=0.003)</td>
<td>18.0 vs 21.1 (P&lt;0.001)</td>
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<td></td>
<td></td>
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<td></td>
<td>CI group II: 69</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Magri et al,29</td>
<td>639</td>
<td>63</td>
<td>87</td>
<td>≤50%</td>
<td>&lt;80% APHR</td>
<td>CI group I: 56</td>
<td>N/A</td>
<td>86% of total cohort taking a BB (n=549)</td>
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<td>CI group II: 82</td>
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<td></td>
<td>CI group II: 88% prescribed BB (n=335)</td>
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<td>CI group II: 82</td>
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<td>CI group II: 88% prescribed BB (n=462)</td>
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<td>CI group II: 82</td>
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<td>CI group II: 76% prescribed BB (n=214)</td>
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<td>CI group II: 76% prescribed BB (n=87)</td>
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<tr>
<td>Jorde et al,25</td>
<td>278</td>
<td>51</td>
<td>100</td>
<td>&lt;40%</td>
<td>&lt;80% APHR</td>
<td>46</td>
<td>N/A</td>
<td>74 vs 71 (P=0.51)</td>
<td>15.4 vs 19.9 (P&lt;0.001)</td>
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<td>CI group I: 69</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Witte et al,30</td>
<td>237</td>
<td>67</td>
<td>100</td>
<td>&lt;40%</td>
<td>&lt;80% APHR</td>
<td>CI group I: 43</td>
<td>2.8</td>
<td>69% of total cohort taking a BB (n=164)</td>
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<td></td>
<td>CI group II: 72% (80/103) taking a BB</td>
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<td></td>
<td>CI group I: 18.6 vs 21.2, P=0.0007</td>
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<td></td>
<td>CI group II: 72% (123/170) taking a BB</td>
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<td></td>
<td>CI group II: 17.8 vs 22.4, P=0.0002</td>
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<td></td>
<td>CI group II: 72% (84/134) taking a BB</td>
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<td></td>
<td>CI group II: 61% (41/67) taking a BB</td>
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</tr>
<tr>
<td>Robbins et al,31</td>
<td>470</td>
<td>52</td>
<td>94</td>
<td>Mean 21%±8%</td>
<td>CIx</td>
<td>Mean CIx 0.71</td>
<td>2</td>
<td>No BB prescribed</td>
<td>N/A</td>
</tr>
<tr>
<td>Clark and Coats,31</td>
<td>57</td>
<td>59</td>
<td>72</td>
<td>Mean 30%</td>
<td>&lt;80% APHR</td>
<td>28</td>
<td>N/A</td>
<td>No BB prescribed</td>
<td>17.6 vs 20.6 (P=0.16)</td>
</tr>
</tbody>
</table>

166
ptients with CHF, 46% (n=128) had CI. Patients who reached a peak VO\textsubscript{2} (pVO\textsubscript{2}) > 20 mL/kg/min had a prevalence of CI of 24% rising to 72% in those with pVO\textsubscript{2} < 14 mL/kg/min.\textsuperscript{25} Such results have led to the widespread perception that CI is a major cause of exercise intolerance in CHF.\textsuperscript{21}

**Does Chronotropic Incompetence Limit Exercise Capacity in Patients with CHF?**

In small studies of patients with coronary artery disease and mild-to-moderate left ventricular systolic dysfunction (LVSD) (mean left ventricular ejection fraction [LVEF] 47%), Lele et al\textsuperscript{26} and Roche et al\textsuperscript{27} found no association between chronotropic competence and exercise capacity (Table II).\textsuperscript{11,25,28-31} Although Roche found that 60% of patients had CI (maximum age-predicted heart rate [MAPHR] <80%), there was no significant difference in pVO\textsubscript{2} between patients with or without CI (17±7 vs 20±6 mL/kg/min,

<table>
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<tr>
<th>Primary outcome(s)</th>
<th>Results</th>
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| Mortality          | No difference in 1-year survival CI vs no CI (54% vs 42%, \(P=0.21\))  
No CI measures independently predictive of survival  
Significant predictors of survival in MV analysis are pVO\textsubscript{2}, age, and BB use |
| Effect of CI on functional capacity and importance of BB therapy | Of patients not prescribed a BB, 29% and 69% had CI  
Of patients prescribed a BB, 61% and 84% had CI (%MAPHR and %HRR)  
Change in heart rate was the strongest variable in the MV analysis to be associated with pVO\textsubscript{2}  
No difference in average dose of BB in patients with or without CI  
Relationship between change in heart rate and pVO\textsubscript{2} reached was similar in patients taking or not taking a BB (r=0.63, \(P<0.0001\) vs \(r=0.57, P<0.0001\)) |
| Prevalence of CI | 72%, 48%, and 24% for patients with pVO\textsubscript{2} <14.0, 14.0-20.0, and >20.0 mL/kg/min, respectively |
| Norepinephrine release Clx\textsuperscript{†} | 1687 (CI) vs 2593 (no CI) pg/mL (\(P=NS\)) (n=24)  
12.7 vs. 22.1 (\(P=0.002\)) (n=24) |
| Prevalence of CI | CI not an independent predictor of survival in a MV model |
| Whether CI affects exercise | Patients prescribed a BB more likely to have CI than patients not taking BB (75% vs 64%, \(P=0.04\)) |
| Whether CI affects prognosis | Patients taking a BB compared with not taking a BB had similar pVO\textsubscript{2}. Patients taking a BB exercised for longer than patients not taking a BB (498 vs 435 seconds, \(P=0.02\)) |
| All-cause mortality | Relationship between pVO\textsubscript{2}, %MAPHR and %HRR similar for patients taking or not taking a BB |
| Correlations between patients with CI and no CI | MV analysis, low Clx (\(\leq 0.51\)) associated with greater mortality (HR, 1.94; 95% CI, 1.18-3.19, \(P=0.009\)). As a continuous variable, for each SD decrease, Clx (HR, 1.40, 95% CI, 1.07-1.79, \(P=0.01\))  
Moderate correlation between peak VO\textsubscript{2} and Clx (r=0.58)  
Weak correlation between Clx and LVSD (r=0.09) |

\(\text{Clx}^\dagger\) Chronotropic responsiveness index = ([baseline heart rate – peak heart rate] / log[baseline norepinephrine– peak norepinephrine]).
**Clinical consequences of chronotropic incompetence in patients with CVD - Callington and others**

*Dialogues in Cardiovascular Medicine - Vol 18 No. 3 2013*

**Clinical consequences of chronotropic incompetence in patients with CVD**

**IT IS NOT THE CAUSE OF EXERCISE LIMITATION**

It might be that CI is the consequence rather than the cause of exercise limitation. In a novel study where patients with CHF (n=11) or control (normal) subjects (n=9) exercised at three submaximal workloads (15%, 25%, and 50% of peak workload), Witte et al. found that although there was an association between absolute workload and heart rate in controls (r=0.85, P<0.0001), there was no such association in patients with CHF (r=0.003, P=0.98) (*Table II*). Comparatively, heart rate at steady state at all three workloads was similar for controls versus patients with CHF (15%, 80 vs 80 beats per minute [P=NS]; 25%, 86 vs 91 per minute [P=NS]; and 50%, 101 vs 109 per minute [P=NS]). Peak heart rate was lower in patients with CHF compared with “controls” (120 vs 159 beats per minute, P=0.0001).

**β-BLOCKERS, CHRONOTROPIC INCOMPETENCE, AND REDUCED EXERCISE TOLERANCE**

Any discussion about the importance of chronotropic incompetence in patients with CHF has to consider the major impact of β-blocker therapy. β-Blockers are a cornerstone of therapy for patients with CHF due to LVSD and are prescribed to around 80% of all patients. Those taking a β-blocker have a lower resting heart rate, a lower peak heart rate on exercise, and an attenuated heart rate response during exercise: they are thus likely to have CI. As a consequence of these effects, it is often thought that β-blockers are a cause of CI and are partly responsible for limiting exercise tolerance.

Witte et al. exercised 237 subjects with CHF (mean LVEF 33%) and found that patients taking a β-blocker (69%) exercised for significantly longer than patients not taking one (498 vs 435 seconds, P=0.02) (*Table II*). Patients on a β-blocker had a higher prevalence of CI (49%, defined as <80% of MAPHR) compared with 32% in those not taking a β-blocker (P=0.04). There was no difference in baseline LVEF or symptom class between the two patient groups. Witte et al. also showed that chronic β-blocker therapy resulted in improvement in exercise time and reduction in exertional breathlessness.

Magri et al. analyzed cardiopulmonary exercise test data from 639 patients with CHF (mean LVEF <40%), 87% of whom were in sinus rhythm, 549 patients were taking a β-blocker and 90 were not. CI was defined by two methods: <80% MAPHR and <80% heart rate reserve (HRR) (*Table II*). Of the total cohort, 56% (n=357) (<80% MAPHR) and 82% (n=524) (<80% HRR) had CI. Patients taking a β-blocker had a similar pVO2 (15.6±4.5 vs 15.7±5.2 mL/kg/min, P=NS) and NYHA functional class to those who were not. Patients taking a β-blocker with CI had a lower pVO2 and worse functional class than patients taking a β-blocker without CI. However, there was no difference in the average β-blocker dose between patients with or without CI. Correlation between the change in heart rate during exercise and pVO2 was similar in patients who were taking a β-blocker (r=0.57, P<0.0001) and in those who were not (r=0.63, P<0.0001).

Although β-blockers may result in a higher prevalence of CI, β-blocker therapy is not associated with any reduction in functional capacity. Jorde et al. studied 278 patients with CHF in sinus rhythm and with a LVEF <40%, of whom 46% had CI (<80% MAPHR) (*Table II*). A similar proportion of patients with or without CI were taking a β-blocker. Patients with CI exercised for a shorter time. The relationship between exercise time and heart rate was examined. This showed that the rate of change of heart rate by a given time (and workload at that point) was slower in patients with CI compared with patients without CI. Whether or not a patient was taking a β-blocker was irrelevant and did not affect the rate of change in heart rate (*Figure 1*). More recently, in a small study of 19 patients with advanced CHF and CI, Hirsh et al. showed that acute withdrawal of β-blocker resulted in a higher heart rate at peak exercise, but this had no effect on pVO2 attained. Withdrawal of β-blocker therapy did not restore chronotropic competence.

**CHRONOTROPIC INCOMPETENCE AND SURVIVAL IN PEOPLE WITHOUT HEART FAILURE**

Ischemic heart disease may cause a reduction in the heart rate response to exercise which may be reversed after revascularization. Not surprisingly, significant coronary artery disease affecting the right coronary artery is independently associated with CI. May be an adaptive response resulting in a longer period in diastole, allowing more time for coronary artery perfusion.

Since the early 1970s, CI has repeatedly been shown to be an independent prognostic indicator of mortality or coronary events in subjects.
with or without cardiovascular disease. In patients without LVSD, CI is associated with a higher prevalence of coronary artery disease, shortened survival and a higher incidence of cardiac events. In a study of men from the Framingham dataset (n=1575) who were in sinus rhythm, without known coronary artery disease or CHF and not taking a β-blocker, approximately one-fifth (n=327) were unable to reach their “target” heart rate (peak exercise heart rate <85% of MAPHR). Over a mean follow-up of almost 8 years, the mortality rate of subjects not reaching “target” heart rate was double that of those without CI (6% vs 3%). However, “failure to achieve target heart rate” was not an independent predictor, suggesting that its presence was merely a marker of low exercise tolerance.

Dresing et al followed up 384 patients over a period of approximately 6 years, who underwent both an exercise stress test and coronary angiography within 90 days. During follow-up, almost 15% died. Only a small proportion of patients (n=41) had a LVEF <40%. A total of 16% (n=61) had CI when defined as an inability to attain 85% MAPHR or 35% (n=133) if defined as being unable to attain 0.8 on the chronotropic index. CI was associated with worse survival. In patients without severe coronary artery disease, the heart rate between rest and 40% of peak workload was not. An increase in heart rate of less than 46 beats per minute between 40 and 100% of peak workload was associated with double the risk of death.

Patients with the combination of inducible myocardial ischemia and CI have a worse prognosis than patients with inducible myocardial ischemia, but no CI. In a study of 2953 patients who underwent myocardial perfusion single-photon emission computed tomography (MPS) using treadmill stress, 11% (n=316) did not attain at least 85% of their MAPHR and 26% (n=762) had a low chronotropic index (<0.8). Both descriptors of CI were predictors of mortality. The highest risk of mortality was for the 8% of patients with both a low chronotropic index and perfusion defects. Similar findings were found in an even larger study of 10,021 patients undergoing exercise stress MPS. Over a mean follow-up of almost 2 years, the risk of cardiovascular death was 3.5% in patients with perfusion abnormalities and low chronotropic index, compared with 1.4% in patients with myocardial perfusion abnormalities alone, and 0.2% risk in patients with normal myocardial perfusion scan and normal chronotropic response. A similar additive risk relationship exists in patients with CI and inducible ischemia on stress echo.

The prognostic importance of CI has been assessed in patients with coronary artery disease who have undergone coronary artery bypass grafting. Girotra et al enrolled 920 patients who had previously undergone bypass grafting, had normal LVEF, patent saphenous vein grafts, and had discontinued β-blockers 48 hours before symptoms limited treadmill testing. Follow-up was over a mean period of 4.2 years.
and 5% of patients died. A threshold chronotropic index of 0.85 was associated with a 49% increase in relative risk for the composite end point of death (nonfatal myocardial infarction, stroke, coronary artery bypass graft (CABG) or angioplasty), and a 71% increase in relative risk of “angiographic complete occlusion.”

**CHRONOTROPIC INCOMPETENCE AND SURVIVAL IN PATIENTS WITH HEART FAILURE**

CI does not appear to be an independent predictor of survival in CHF patients as it is usually “knocked out” in multivariate analysis by other exercise variables such as pVO2, VE/VC02 slope or even simply exercise duration. In an analysis by Al-Najjar et al of 411 patients with CHF who underwent CPET (83% with moderate LVSD or worse), CI (inability to achieve ≥80% MAPHR) was found in 42% (Table II). The mean follow-up was 7.4 years, and 157 patients died (38%). Patients with CI, compared with those without CI, exercised for a shorter time (424 vs 510 seconds) and had a lower pVO2 (18 vs 21.1 mL/kg/min). CI was not a predictor of mortality (Figure 2).28

In a post hoc analysis of 1118 patients with at least moderate LVSD enrolled in the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of exercise training) study, Dobre et al suggested that there may be a nonlinear relationship between heart rate response to exercise and survival. Patients with a chronotropic index of <0.6 had a mortality risk that increased exponentially as the chronotropic index fell. Above the 0.6 threshold, the index was not an important predictor of prognosis. Each reduction in chronotropic index by 0.1 was associated with a 17% relative increase in all-cause mortality and a 13% relative increase in cardiovascular mortality or hospitalization due to heart failure.

In a study population that predated recommendations for β-blocker therapy as usual care, Robbins et al reported on 470 patients referred for possible heart transplant (Table II). The mean LVEF was 21%±8% and most (94%) were in sinus rhythm, average pVO2 was 18±6 mL/kg/min. Patients who were taking a β-blocker were excluded from the study. Follow-up was for 18 months, and 15% of patients died (n=71). The chronotropic index was used as the chosen marker of CI. Patients with a chronotropic index ≤0.51 had worse survival than patients with values over 0.51. For each standard deviation decrease in CI there was a 40% relative increase in risk of death (HR 1.40; 95% CI, 1.06-1.85; P=0.02). Unusually, pVO2, usually one of the strongest predictors of survival for patients with CHF, was not a significant independent prognostic indicator.53

The various definitions of CI, which arbitrarily dichotomize patients into those with or without CI, are an oversimplification. Heart rate response to exercise is a continuous variable. A measure of whether a diagnostic cut-off has any value is when a patient labeled as “diagnosis positive” derives some benefit from a treatment that can correct the problem. If CI is truly an independent risk factor for worse outcome, then restoration of chronotropic response, perhaps by pacing, should reduce mortality. Smaller trials have shown that improving the chronotropic response by pacing can marginally increase distance walked during a 6-minute walk test. Such small improvements have not translated into long-term symptomatic benefits.
benefit or longer survival. Conventional right ventricular pacing may be deleterious, so the better option is pacing delivered by atrial stimulation alone or by biventricular pacing.\(^5^7\)

There are few studies to indicate whether increasing the heart rate response might be helpful. In the PEGASUS CRT study (Pacing Evaluation-Atrial Support Study in Cardiac Resynchronization Therapy), 1433 patients with cardiac resynchronization devices were randomized into control (DDD-40), DDD-70, or DDDR-40 arms. There was no difference in the composite outcome (comprising all-cause mortality, heart failure events, NYHA class, and self-assessment scores) between any of the pacing groups.\(^5^8\)

**CHRONOTROPIC INCOMPETENCE, CHF, AND ATRIAL FIBRILLATION**

Approximately 30% to 40% of patients with CHF have atrial fibrillation (AF). As the severity of heart failure worsens, the prevalence of AF increases. "Atrial kick" is lost in patients with AF, and it may be that resting and exercise heart rates need to be higher than in patients in sinus rhythm to maintain adequate cardiac output.\(^5^9\)\(^-\)\(^6^1\)

For some patients in AF, the electrical rate is not identical to the pulse rate at the wrist, making determination of CI even more difficult to define. Patients in AF usually have a higher resting heart rate compared with patients in sinus rhythm and usually have a higher maximum heart rate at peak exercise (approximately 20 to 30 beats per minute faster).\(^6^2\) As the definitions of CI were constructed for patients in sinus rhythm, the prevalence of CI will be, in general, much lower for people in AF.

Al Najjar et al found that 28% of patients with AF and CHF had CI compared with 53% of patients who were in sinus rhythm.\(^5^3\) Similarly, Fei et al found that approximately a quarter of their 41 patients with CHF (mean LVEF <30%) and AF had CI (inability to achieve ≥80% MPHR).\(^5^4\) Van den Berg et al assessed 73 patients with AF using treadmill CPET, none of whom had CHF.\(^6^4\) Interestingly, patients who reached a lower pVO\textsubscript{2} had a higher heart rate in the early stages of exercise, but a lower heart rate at peak exercise.

The importance of resting heart rate as a prognostic indicator in patients with CHF and AF remains unknown, but current evidence suggests that resting heart rate may not be as important as for patients in sinus rhythm. There is no definition of CI specifically in patients with AF, so it is difficult to make any conclusions regarding its value in predicting survival.

**CONCLUSIONS**

The relationship between chronotropic incompetence, exercise capacity, and prognosis is still unclear. The lack of clarity is largely due to the lack of a robust definition of CI that is not at the same time simply a surrogate of exercise capacity. During an incremental exercise test, many variables increase: heart rate, respiratory rate, and oxygen consumption, and do so, more-or-less, as a function of exercise intensity and hence, duration. They will all, therefore, necessarily correlate with one another. The more intense the workload, the greater the heart rate response will be. It is a foregone conclusion that patients who reach a lower maximal exercise intensity will have a lower peak heart rate. As peak exercise capacity correlates with peak heart rate, peak heart rate (or change in heart rate) will inevitably relate to prognosis. Rather than categorizing patients by an arbitrary definition, perhaps CI is represented better by assessing the correlation slope between heart rate and exercise load or duration of exercise. A person with CI will have a shallower heart rate/exercise load slope, ie, at a given exercise load they will have a lower heart rate and a slower increase in rate.

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CHRONOTROPIC INCOMPETENCE (CI) is defined as an inadequate heart rate (HR) response to exercise. The increase in HR during exercise is the strongest contributor to the increase in cardiac output and to the ability to perform maximal exercise. Hence, CI has a major role as a cause of symptoms and exercise intolerance. CI is also an independent prognostic factor for adverse cardiovascular events and mortality, and this has been shown in normal subjects, patients with coronary artery disease, and patients with heart failure (HF). The prognostic role of CI is likely caused by its association with autonomic dysfunction and reduced β-adrenergic sensitivity. Correction of CI is therefore a potential therapeutic target to improve exercise tolerance and symptoms and possibly also patient prognosis.

Drug treatment of cardiovascular diseases may have a major role for the control of HR. However, as outlined below, it does not seem to have a major effect on the rate of CI As CI plays a particularly important role in patients with HF and as most studies relate to β-blocker therapy, we will focus on these two aspects in the following chapters.

EFFECTS OF β-BLOCKERS IN PATIENTS WITH HEART FAILURE AND REDUCED EJECTION FRACTION

Many cardiovascular drugs, such as digoxin, β-blockers, verapamil, diltiazem, amiodarone, and more recently, ivabradine, reduce HR at...
rest and during exercise. In patients with HF, the reduction in HR response to exercise after long-term β-blocker therapy is a major cause of lack of improvement in exercise tolerance, despite the improvement in peak exercise cardiac function and stroke volume. Several studies in HF patients treated with β-blockers have also evidenced a direct correlation between the magnitude of HR reduction at peak exercise and HF. In these studies, β-blocker therapy, compared with control conditions, is also associated with the expected reduction of HR at rest and during exercise, as well as with a similar exercise intensity and a similar sensitivity to adrenergic drive, as shown by the ratio between plasma norepinephrine and HR during exercise, and with increased efficiency, as shown by the lower oxygen pulse.

Thus, CI does not seem to be caused by β-blocker therapy independently from the reduction in peak exercise HR. Its main causes are likely the intrinsic anatomic and functional changes in the sinus node, β₁-adrenergic receptor downregulation, and reduced sensitivity to adrenergic drive. Thus, although β-blockers may impair the chronotropic response to exercise, and hence, not improve exercise tolerance in patients with HF, they do not cause CI, which is associated with the progression of HF (Figure 1). β₁-Adrenergic receptor upregulation, and more generally, improved cardiac function after long-term β-blocker treatment, may actually be associated with reduced CI, as shown in a recent study.

**EFFECTS OF β-BLOCKERS IN PATIENTS WITH HEART FAILURE AND PRESERVED EJECTION FRACTION**

The majority of patients with HF have preserved left ventricular (LV) ejection fraction and their proportion is increasing due to aging of the general population. Patients with heart failure with preserved ejection fraction (HFP EF) exhibit similar impairment of exercise tolerance and symptoms, compared with patients with heart failure with reduced ejection fraction (HFREF). The pathogenetic mechanisms are, however, different. In a landmark study, Boilaug et al showed that patients with HFP EF had marked impairment in exercise tolerance compared with subjects without symptoms of HF, but with similar age, sex, and prevalence of diabetes, obesity, hypertension, and LV hypertrophy. Exercise capacity correlated with the change in cardiac output, heart rate, and vascular resistance, but not with end-diastolic volume or stroke volume. These data have been confirmed by further studies showing a similar proportion of patients with CI among those with HFREF and HFP EF with almost 3-fold the prevalence found in normal subjects.

Recent results are consistent with the hypothesis that CI is a major cause of exercise intolerance in the patients with HFP EF and that these patients are particularly sensitive to the negative chronotropic effects of β-blocker therapy. The effects of the β-blocker nebivolol on exercise tolerance in patients with HFP EF were assessed in a multicenter, placebo-controlled trial. Nebivolol was tested because its effects on nitric oxide release were thought to induce myocardial relaxation and LV filling during exercise. However, compared with placebo, after 6 months of treatment no associa-
tion was found between nebivolol and improvement in 6-minute walking distance (from $420 \pm 143$ to $428 \pm 141$ meters with nebivolol versus from $412 \pm 123$ to $446 \pm 119$ meters with placebo, $P=0.004$ for interaction) or change in $\text{pVO}_{2}$ (from $17.0 \pm 4.8$ to $16.3 \pm 3.8 \text{ mL/kg/min}$ with nebivolol versus from $17.8 \pm 6.0$ to $18.6 \pm 5.6 \text{ mL/kg/min}$ with placebo, $P=0.63$ for interaction). Interestingly, a direct correlation was found between the change from baseline in $\text{pVO}_{2}$ and that of HR at peak exercise (Figure 2). Thus, the negative chronotropic effects of nebivolol explain the lack of improvement in exercise tolerance despite the associated favorable properties of this agent.

EFFECTS OF HEART RATE REDUCTION WITH OTHER AGENTS

Tachycardia has an unfavorable effect on prognosis. HR reduction is therefore a major target of treatment of cardiovascular disease and, in particular, HF. Calcium antagonists are contraindicated in patients with HFREF and, thus there are no large studies with these agents. The effects of verapamil on exercise tolerance were assessed in a small study in 20 patients with HFREF with a placebo-controlled, double-blind, 5-week crossover design. Compared with baseline, verapamil was associated with an improvement in exercise duration (from $10.7 \pm 3.4$ to $13.9 \pm 4.3$ minutes; $P<0.05$), peak filling rate, and HF score. No further studies, however, were conducted, with either verapamil or diltiazem.

More recently, the heart rate–reducing agent ivabradine has been associated with a significant reduction in the combined end point of cardiovascular death or HF hospitalization in patients with HFREF. Interestingly, ivabradine has a specific inhibitory action on the sinoatrial node $I_{f}$ current, with no effects on other cardiac channels or on atrioventricular conduction or myocardial contractility. Its heart rate–reducing action is HR-dependent, being greater in those subjects with higher HR. This may contribute to its favorable effects reported in SHIFT (Systolic Heart failure treatment with $I_{f}$ inhibitor ivabradine Trial) on quality of life, with larger effects in patients with higher HR at baseline. Two smaller studies have reported beneficial effects of ivabradine on CI versus $\beta$-blockers on exercise tolerance, and on CI.
EXERCISE TRAINING

To date, exercise training is the treatment that has been most consistently associated with beneficial effects on the HR response to exercise. This is consistent with the observation that CI is a sign of autonomic dysfunction and with the efficacy of exercise training on sympathovagal balance. Training is associated with decreased sympathetic drive and increased vagal stimulation, baroreflex sensitivity, and HR variability. Both in normal subjects as well as in patients with HFREF, exercise training has been associated with favorable effects on HR response to exercise and decreased resting and submaximal exercise HR, and a more rapid decline in postexercise HR. Interestingly, peak exercise HR is slightly increased after aerobic training, with a 5% to 7% increase in most of the studies (Figure 3, page 177).²¹-²⁴

In a study in 51 patients with HF, randomized to aerobic training or no exercise, training was associated with an increase in peak exercise HR of 9±3 beats/min, compared with 1±3 beats/min, in the control group. A larger increase from baseline was found in the patients with CI (Figure 4) and a significant and direct correlation was found between the change from baseline in the peak exercise HR and the change in pVO₂, showing the contribution of improved chronotropic response to exercise to improved exercise tolerance in these patients.²⁵

Patients with HFPEF have similar symptoms and exercise intolerance to patients with HFREF. No treatment has been proven to be effective in these patients, to date. However, a recent randomized, attention-controlled, single-blind study of medically supervised exercise training in 53 elderly patients with isolated HFPEF showed an increase in pVO₂ in the exercise-training group (13.8±2.5 to 16.1±2.6 mL/kg/min associated, also in this study, with an increase in peak exercise HR from 133±20 to 137±16 beats/minute versus from 136±18 to 129±20 beats/minute in the control group).²⁶ Thus, improvement in autonomic balance and HR response to exercise after aerobic training directly contribute

Figure 4. Percent change in peak exercise heart rate at week 24 among patients with and without chronotropic incompetence (CI). Values are given at baseline in the control group and in the exercise-training group.

to increased cardiac output response to exercise and hence improvement in exercise tolerance in patients with HF.

**RATE-ADAPTIVE PACING**

Though probably not able to correct the intrinsic sinus node abnormalities causing CI, rate-adaptive pacing may be the best tool to correct CI. Its target is to improve the HR response to exercise and increased demand, ie, CI. Despite its potential as a tool to improve exercise tolerance, symptoms, and quality of life, it has not been a major focus of research during these past years, probably because research overwhelmingly concerned devices for cardiac resynchronization therapy (CRT), defibrillation techniques, and telemedicine. The difficulties and the variability in the definition and, from some points of view, in the assessment of CI, have likely contributed to a large extent.

Tse et al implanted a rate-responsive pacemaker in 20 patients with HF and CI. All patients underwent a cardiopulmonary exercise treadmill test using DDD mode (for complete explanation of the NBG Pacemaker Code, see reference 28) with fixed atrioventricular interval (DDD-OFF). DDD mode with adaptive atrioventricular interval on (DDD-ON), and DDDR (rate-responsive) mode with adaptive atrioventricular interval on (DDDR-ON). In patients with CI at baseline, the DDDR-ON mode, compared with the DDD-OFF and DDD-ON modes, was associated with an increase in peak exercise HR, peak exercise time, peak exercise workload, and pVO₂ (P<0.05). In contrast, there were no significant differences between the different pacing modes in the patients with no CI at baseline. The percentage or HR changes during exercise positively correlated with exercise time, peak workload, and pVO₂, confirming that an increase in the HR response to exercise may increase cardiac output and exercise tolerance (Figure 5).

In another study, 13 patients with HF, a CRT device, and severe CI, were randomized in a double-blind crossover pilot study to either DDD or DDDR pacing. DDDR pacing was associated with an acute improvement in the 6-minute walking test distance (from 358.5±40.7 to 376.8±24.5 meters; P=0.05) with no significant change in pVO₂. In addition, the DDDR mode was effective in increasing HR response to exercise in only 9 of 13 patients.

A larger (compared with previous studies) controlled study of rate-responsive pacing in patients with HFPEF is now ongoing. As outlined above, HFREF is a frequent condition and CI plays a major role as a cause of exercise intolerance in these patients. The RESET study (Restoration of chronotropic competence in heart failure patients with normal Ejection fraction) is a prospective, multicenter, double-blind, study assessing the effect of rate-responsive cardiac pacing on pVO₂ and quality of life in 400 patients with CI. Patients are also stratified on the basis of β-blocker use with different thresholds for CI according to the use of these agents (percent of age-predicted HR reserve during maximal exercise of ≤80% and ≤62% in those without and with β-blockers, respectively).

**CONCLUSIONS**

Chronotropic incompetence (CI) is a major cause of exercise intolerance and an independent prognostic factor for cardiovascular events, and its treatment constitutes a major therapeutic target, in addition to reducing resting HR, and improving HR response to exercise. β-Blockers reduce HR at rest and during exercise, and do not seem to cause CI. The major causes of CI involve intrinsic sinus node dysfunction and reduced β₁-adrenergic receptor density and sensitivity. Exercise training remains the most effective tool to improve HR response to exercise, with a concomitant improvement in exercise tolerance and quality of life. Rate-adaptive pacing is another potential tool to treat CI, but further studies are needed to confirm this point.

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What are the therapeutic implications of chronotropic incompetence in patients with CVD? - Metra


Chronotropic Incompetence

Summaries of Ten Seminal Papers

Peter Brubaker, PhD; Dalane W. Kitzman, MD

Department of Internal Medicine (Cardiology) - Wake Forest School of Medicine - Winston-Salem
North Carolina - USA (e-mail: dkitzman@wfubmc.edu)


1. Regulation of stroke volume during submaximal and maximal upright exercise in normal man
   M. B. Higginbotham and others. Circ Res. 1986

2. Effect of aging, sex, and physical training on cardiovascular responses to exercise
   T. Ogawa and others. Circulation. 1992

3. Impaired heart rate response to graded exercise: prognostic implications of chronotropic incompetence in the Framingham Heart Study
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6. Heart rate recovery after exercise is a predictor of mortality, independent of angiographic severity of coronary disease
   D. P. Vivekananthan and others. J Am Coll Cardiol. 2003

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10. Resting heart rate and heart rate reserve in advanced heart failure have distinct pathophysiologic correlates and prognostic impact…
    J. Benes and others. JACC Heart Fail. 2013

Selection of seminal papers by D. W. Kitzman, MD
Department of Internal Medicine (Cardiology) - Wake Forest School of Medicine - Winston-Salem - North Carolina - USA

Highlights of the years by Ian Mudway, MD
Lung Biology - Division of Life Sciences - Franklin Williams Building
150 Stamford Street - London SE1 9NN - UK

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Regulation of stroke volume during submaximal and maximal upright exercise in normal man

M. B. Higginbotham, K. G. Morris, R. S. Williams, P. A. McHale, R. D. Coleman, F. R. Cobb


Higginbotham et al in their truly classic seminal work utilized robust techniques (invasively obtained measures of pressures, flows, and volumes) in order to determine the specific components of the integrated physiological response that allows healthy persons to perform upright, maximal exercise. Peak oxygen consumption (VO_{2peak}) is the most objective measure of peak exercise performance (capacity), is reproducible, and is clinically meaningful. The Fick equation for oxygen indicates that VO_{2peak} is the product of cardiac output (which in turn is the product of heart rate and stroke volume) and arteriovenous oxygen difference. This study performed precise, robust measures of each of these 3 factors that determine VO_{2peak} during supine rest, upright rest (seated on a stationary bicycle), and during progressive exercise to exhaustion.

There were several observations that were relevant to the topic of chronotropic incompetence. As shown by others, in the supine position, preload (pulmonary wedge pressure and end-diastolic volume) were near maximal. When subjects assumed the upright rest position, end-diastolic volume and pulmonary wedge pressured declined (about 30%) due to venous pooling in the lower extremities. This decrease in preload caused an approximately 15% decline in stroke volume (contractility increased to partly compensate). This decrease in stroke volume was accompanied by a compensatory increase in heart rate of about 15%, likely driven by increased adrenergic drive. This interaction between end-diastolic volume, stroke volume, and heart rate has been described in many other physiologic and non-physiologic conditions, including pacing, and means that cardiac output at rest is determined by metabolic needs and is modulated partly by an inverse relationship in changes in preload and heart rate, classic response to orthostasis is one such manifestation.

During progressive upright exercise, preload increases, particularly during early stages, in response to the “muscle pump” in the calves, which liberates venous pooling and pushes blood back into the central circulation. During this time of asymptotic increase in preload, there is a linear increase in heart rate with workload and VO_{2peak}. However, this study found a novel, previously unknown phenomenon. After the initial sharp rise in preload (end-diastolic volume) early during exercise, end-diastolic volume response increased no further despite increasing workloads. All increases in stroke volume were therefore caused by increased contractility (decreased end-systolic volume). However, near peak exercise, end-diastolic volume decreased mildly, and was accompanied by a smaller decline in stroke volume. The investigators wondered whether this was an artifact since it had not been previously described. However, this has now been reproduced by others. It has been hypothesized that this mild decline in stroke volume near terminal exercise is due to decreased left ventricular filling, due to shortened filling time. This design makes sense, since continued increases in heart rate produce greater increases in cardiac output than increased stroke volume. Thus, stroke volume is sacrificed in order to allow continued linear increases in heart rate to maximize cardiac output and VO_{2peak}.

Thus, there is a complex interplay between heart rate and end-diastolic volume during orthostatic change and progressive upright exhaustive exercise. This is characterized by an initial drop in end-diastolic volume from supine to the upright position, a sharp increase in end-diastolic volume early during exercise, followed by a flat response, and a slight decline at peak exercise. Heart rate response is linear during exercise, and when needed, end-diastolic volume gives way to allow maximal heart rate and cardiac output.

First-class cricket debut of West Indian fast bowler Curtly Ambrose; Haiti’s President Jean-Claude Duvalier flees to France and Henri Namphy becomes the new leader of Haiti; and the Voyager 2 spacecraft performs the first flyby of Uranus, discovering 11 new moons.
Effect of aging, sex, and physical training on cardiovascular responses to exercise

T. Ogawa, R. J. Spina, W. H. Martin, W. M. Kohrt, K. B. Schechtman

Circulation. 1992;86:494-503

This study showed that reduced heart rate is the primary determinant of the age-related decline in exercise capacity in humans. The ability to perform physical work decreases significantly and inexorably with advancing age, independent of sex. It can be retarded by maintaining habitual exercise, and is accelerated by sedentariness and a variety of specific diseases, as well as obesity. Maximal physical work can be quantified as peak exercise oxygen consumption (VO₂). It had been known that in humans, the determinants of VO₂ included heart rate, stroke volume, and arteriovenous oxygen difference. However, there was uncertainty regarding which of these, or all, were the key determinants of the age-related decline in peak VO₂.

The elegant study by Ogawa et al performed careful measurements of each of these factors in over 100 healthy subjects, including healthy younger and older sedentary and endurance exercise–trained men and women. They found that over a 30-to-40–year range, there was a 40% lower peak VO₂ in older rather than younger subjects, which was attenuated to 25% to 30% in trained subjects. Smaller left ventricular stroke volume accounted for about 50% of the age-related difference in peak VO₂. Importantly for the focus of the present treatise, lower maximum heart rate accounted for the remainder of the difference in VO₂. Thus, lower peak heart rate with aging is a uniform finding and has physiological consequences in that it is a major determinant of the decline in the ability to perform prolonged, exhaustive work. This general finding of reduced peak heart rate with aging has been seen in every study that has examined it and appears to be a universal aging phenomenon.

The investigators also found that the effects of age on maximal heart rate were similar in men and women. Furthermore, maximal heart rate was higher in men and women who were endurance trained. The investigators also found that maximal heart rates were similar in men and women, both trained and untrained. Since VO₂ was lower in women, this indicated that lower stroke volume was responsible for the reduced VO₂.

The mechanisms of this age-related decline are not well understood. It is known that despite lower heart rate, circulating catecholamines at rest and during exercise are increased with age, such that it is not due to reduced adrenergic drive, but rather to reduced adrenergic sensitivity. There may be autonomic contributors. In addition, it is known that the decline in maximal heart rate is associated with a reduced number of pacemaker cells in the heart.

The 25th Olympic Summer games in Barcelona end; the Kristiansund Mainland Connection between the Norwegian mainland, the city of Kristiansund, and the neighboring islands of Frei, Bergsøya, and Aspøya, opens; and millions of black South Africans participate in a general strike to protest about the lack of progress in negotiations between the ANC and the South African government.
Impaired heart rate response to graded exercise: prognostic implications of chronotropic incompetence in the Framingham Heart Study

M. S. Lauer, P. M. Okin, M. G. Larson, J. C. Evans, D. Levy

_Circulation_. 1996;93:1520-1526

While the relationship between impaired autonomic nervous system function and increased mortality was first recognized more than 30 years ago, there was a resurgence of interest, primarily using heart rate variability (HRV) measures, in this topic in the 1990s. Although not without limitations, HRV has been shown to provide important prognostic information in survivors of myocardial infarction as well as in healthy adults in the Framingham Heart Study. With the objective of evaluating a more simplistic measure of autonomic function, these authors proposed to determine the relationship between heart rate (HR) response to exercise and prognosis in asymptomatic subjects from the Framingham Offspring Study.

Members of the Framingham Offspring Study underwent follow-up examinations 8, 12, and 16 years after their initial examination. At each visit, subjects underwent a physician-obtained medical history, a physical examination, an exercise treadmill test according to the Bruce protocol, and fasting blood tests. Exclusion criteria included the presence of coronary heart disease at baseline assessment and use of β-blockers. The analysis was restricted to men as there were very few deaths in the women studied. A total of 1575 men were subsequently followed for a mean of 7.7 years for all-cause mortality and incident coronary heart disease events. HR response during the exercise test was assessed three ways: (i) ability or failure to achieve the target HR (ie, 85% of age- and sex-predicted maximum); (ii) actual increase in HR from rest to peak exercise; and (iii) the ratio of HR to metabolic reserve in stage 2. The later, often called chronotropic response index (CRI), considers that HR during submaximal levels must take into account age, resting HR, and exercise capacity. In healthy subjects, the ratio of HR to metabolic reserve should be approximately 1.0 during submaximal exercise. A low CRI ratio implies chronotropic incompetence and autonomic nervous system imbalance. End points of this study were all-cause mortality and incident coronary heart disease. During a mean follow-up of 7.7 years, there were 55 deaths and 95 incident coronary heart disease events. The inability to achieve target HR and a lower CRI was related to a higher incidence of all-cause mortality and coronary heart disease events, particularly at ≥2 years of follow-up. This increased risk of death and coronary heart disease was present even after considering ST-segment response to exercise, baseline physical activity level, and traditional coronary heart disease risk factors. Another interesting finding of this study was the assessment of a possible J-shaped curve (in which subjects with excessive heart rate response in early exercise might be at increased risk). These analyses determined that a chronotropic response index of ≥1.3 did not increase the risk of achieving the study outcomes. Thus, an attenuated, but not augmented, HR response to exercise represents a simple surrogate measure of autonomic dysfunction that is predictive of increased mortality and coronary heart disease. Assessment of chronotropic response to exercise is a simple noninvasive measurement that adds additional prognostic information to a standard exercise stress test.

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1996

Suspected “Unabomber” Theodore Kaczynski is arrested at his cabin in Montana; the European Union officially recognizes the Federal Republic of Yugoslavia; and British Golfer Nick Faldo wins the 60th Golf Masters Championship.
Effects of exercise training on chronotropic incompetence in patients with heart failure

S. J. Ketyian, C. A. Brawner, J. R. Schairer, T. B. Levine, A. B. Levine, F. J. Rogers, S. Goldstein

Am Heart J. 1999;138:233-240

The ability to perform physical work is an important determinant of quality of life and is enabled by an increase in total body oxygen uptake (VO₂). During maximal aerobic exercise in healthy humans, VO₂ 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, while often overlooked and underappreciated, is actually the strongest contributor to our ability to perform sustained aerobic exercise. In addition to an impaired stroke volume response to exercise, patients with heart failure (HF) often demonstrate an attenuated HR response, resulting in a further reduction in cardiac output and VO₂ at peak exercise (VO₂peak). Endurance exercise training generally results in a significant (10% to 30%) increase in VO₂peak in both healthy subjects and HF patients. In healthy subjects, peak exercise HR generally remains the same or slightly decreases after exercise training, allowing for adequate/enhanced diastolic filling time. The effect of exercise training on HR response of HF patients has not been well studied.

Using a prospective randomized design, the authors examined the effects of 24 weeks of aerobic exercise training on peak HR in patients with heart failure as well as to what extent change in HR during exercise contributes to changes in exercise tolerance. This study also examined the effects of sinoatrial node responsiveness, a potential mediator of chronotropic responsiveness. The inclusion criteria for this study were: (i) NYHA class II or III, (ii) no change in medical therapy for 30 days prior to testing, and (iii) a resting ejection fraction (EF) ≥55%. It is important to note that while medical therapy of the participants was “stable” and unchanged during the 24-week period, this study was conducted in the late 1990s and only 7% of the participants were on a β-blocker, a number well below what is now observed in contemporary studies. Also, this trial did not include any patients with HF and preserved EF. The 51 participants were randomized to an exercise training (ET) group or to a nonexercise control (CON) group. The ET intervention was fairly standard at the time, with participants performing a total of 33 minutes of exercise (divided evenly among 3 modes of exercise) using the heart rate reserve method to regulate exercise intensity at 50% to 80%, as tolerated, for a total of approximately 72 sessions. Exercise testing was performed before and after the 24-week intervention in a standard fashion on a cycle ergometer with chronotropic incompetence (CI) defined as the inability to achieve a peak HR of >85% of the age-predicted maximum on baseline tests.

The results indicate that peak HR increased significantly in the ET group (9±3 beats/min ≈7%) vs CON (1±3 beats/min) and that the change in peak HR was more pronounced in ET patients with CI (12±3 beats/min) at baseline. The training induced an increase in mean peak HR, which accounted for an astounding 50% increase in mean VO₂peak in the ET group—a value much higher than the 20% to 25% that our group and others have observed. Surprisingly, there were no significant changes in plasma norepinephrine levels at rest, submaximal, or peak exercise in the ET group. Moreover, the ratio of HR reserve to norepinephrine reserve, an indirect index of sinoatrial sympathetic responsiveness, was not changed in either the ET or CON groups. While this study has several important limitations, results suggest, for the first time, that ET may potentially improve chronotropic responsiveness in HF patients, particularly those with CI. The specific mechanism(s) responsible were then, and still are today, unclear. Clearly more research to evaluate the impact of ET on chronotropic response and other interventional therapies is warranted, particularly with the inclusion of women, the elderly, and patients with HF and preserved EF.

Chechen guerrillas invade the Russian republic of Dagestan, triggering a short war; East Timor votes for independence from Indonesia; and Russian President Boris Yeltsin fires his Prime Minister, Sergei Stepashin
Maximal heart rate (HR_{max}) is commonly used as the basis for prescribing exercise intensity in rehabilitation and disease prevention programs as well as a criterion for achieving maximal exertion during exercise testing. Since maximal exercise testing is not feasible in many settings, HR_{max} is often estimated using the age-predicted equation of 220-age. However, the validity of this equation, although widely used since the 1970s, was never established, particularly in study samples including an adequate number of older adults.

The aim of this study was to determine an equation for predicting HR_{max} in healthy, nonmedicated humans that ranged widely in age. To accomplish this, the authors first used a meta-analytic approach in which group mean HR_{max} values were obtained from published studies. Subsequently, a newly derived equation was cross-validated in a well-controlled, laboratory-based study. This study also sought to determine if sex and/or habitual physical activity status exerted significant modulatory influences on the HR_{max}-age equation. The meta-analysis portion of the study used well-defined inclusion criteria and ultimately included 351 studies for a total of 18,712 subjects. The meta-analysis indicated that HR_{max} was strongly and inversely related to age in both men and women (r=-0.90). The rate of decline and the y-intercepts were not different between men and women or among sedentary, active, and endurance-trained subjects. The regression equation, with all subjects combined, was 208-0.7\times age. Stepwise regression analysis revealed that age alone explained approximately 80% of the individual variance in HR_{max}.

In the cross-validation study of the derived equation, 514 apparently healthy, nonobese subjects (237 men and 277 women) between the ages of 18 and 81 years were studied in a controlled laboratory environment. HR_{max} was determined by a continuous, incremental treadmill protocol. Heart rate was continuously monitored by ECG and oxygen consumption was measured using standard methods. HR_{max} was defined as the highest value recorded during the test. To ensure that maximal exertion was obtained, at least three of the following four commonly used criteria had to be achieved during the test: (i) a plateau in oxygen consumption despite an increase in workload; (ii) a respiratory exchange ratio of \geq 1.15; (iii) a maximal respiratory rate of \geq 35 breaths/minute; and (iv) a rating of perceived exertion of \geq 18 on the Borg scale. HR_{max} was inversely related to age in both men and women. There was, as expected, substantial variation in HR_{max} across the entire age-range, with standard deviations ranging from 7 to 11 beats/min. Thus, practitioners must recognize that no equation provides a perfect prediction and need to consider this variability when employing age-related HR_{max} equations.

Unfortunately, as is often the case, “old habits die hard” as many practitioners still rely on the traditional 200-age equation despite its limitations and the development of this more valid and generalizable equation. When comparing the 220-age formula to the formula derived by Tanaka and colleagues, the former equation overestimates HR_{max} in subjects \leq 40 years, but underestimates HR_{max} in older adults. In subjects \geq 70 years, this may amount to a 10-to-20 beat/minute difference. Consequently, the Tanaka formula of 208-0.7\times age should be utilized, particularly when working with older adults in exercise testing or prescription environments.
Heart rate recovery after exercise is a predictor of mortality, independent of angiographic severity of coronary disease

D. P. Vivekananthan, E. H. Blackstone, C. E. Pothier, M. S. Lauer

J Am Coll Cardiol. 2003;42:831-838

Immediately after the cessation of physical exertion, sympathetic nervous system withdrawal, and more importantly, reactivation of the parasympathetic nervous system, normally cause a rapid decline in heart rate. Abnormal heart rate recovery (HRR), indicative of reduced vagal activity, has been shown to adversely impact a variety of patient populations even after accounting for myocardial ischemia, chronotropic incompetence, and Duke treadmill score. However, there are few data on the prognostic significance of HRR once the angiographic severity of coronary artery disease (CAD) is ascertained.

For this investigation, a cohort of 2935 adults referred for inaugural symptom-limited treadmill testing at the Cleveland Clinic between 1990 and 1998 was followed for a median of 6 years. Patients were eligible if they underwent coronary angiography within 90 days and were free of heart failure, valvular disease, preexcitation, congenital disease, coronary interventions or surgery, pacemaker placement, use of digoxin, or atrial fibrillation. Severity of CAD and left ventricular function were determined by cardiologists blinded to patients’ HRR values and the study hypotheses. Exercise testing was conducted in a standard fashion on a treadmill with stress echocardiography being performed in 509 (17%) subjects. HRR was calculated from the difference in heart rate from peak exercise to 1 minute afterward. Based on previously published data, abnormal HRR was defined as ≤12 beats/min for standard exercise testing (with an “active” recovery period) and ≤18 beats/min for patients that underwent stress echocardiography (with a “passive” recovery period). All-cause mortality, an unbiased and objective end point, was assessed during a median follow-up period of 6 years.

Results from this investigation indicate that patients with abnormal HRR were older and more likely to have hypertension or diabetes, a history of myocardial infarction, chronotropic incompetence, or abnormal ST-segment changes. Patients with abnormal HRR were more likely to have severe CAD, yet abnormal HRR had a sensitivity of only 31% and a specificity of 76% for the detection of any CAD. During the median follow-up period of 6 years, there were 336 deaths (11%). Abnormal HRR was a univariate predictor of mortality along with older age, severe CAD, low ejection fraction percent, poor functional capacity, chronotropic incompetence, and male sex. The multivariable Cox regression analysis indicated that even after adjusting for numerous demographic and prognostic factors, including the angiographically determined CAD severity, a low HRR still emerged as a strong predictor of death (adjusted HR of 1.6). Neither sex nor β-blocker use had any impact on the association between HRR and mortality. This study suggests that not only was the mortality risk of having an abnormal HRR comparable to having angiographically severe CAD, but that this relatively simple noninvasive measurement can provide additive prognostic information. These findings provide evidence that HRR assessment should be incorporated into the routine interpretation of exercise stress test data. Failure of HR to drop by 12 beats/min or more after 1 minute of active recovery (≤18 beats/min if recovery is passive) from an exercise stress test should be of concern and warrant further clinical assessment.

2003

Belgian tennis player Justine Henin-Hardenne defeats her fellow countrywoman Kim Clijsters to win her first US Open title; country singing legend Johnny Cash dies at the age of 71 from complications arising from diabetes; and thousands of protesters march in major cities around the world to protest against the US-led invasion of Iraq.
Determining an individual's age-predicted maximal heart rate (HR) has important applications in clinical settings including: (i) determining the physiologic stress during an exercise test; (ii) the basis for prescribing the appropriate exercise intensity; and (iii) to identify the presence of chronotropic incompetence. While several equations have been developed for this purpose, the most common is 220-age, none have been developed specifically for individuals with coronary heart disease and/or for those taking β-adrenergic blockers. An equation, specific to this patient population, would be very valuable as these patients are commonly referred for exercise stress testing and exercise training programs.

Using their own large database, these authors identified patients between the ages of 40 and 80 with a history of myocardial infarction and/or revascularization, preserved left ventricular function, in sinus rhythm, and achievement of a respiratory exchange ratio of ≥1.10. Excluded patients included those with angina and/or ischemic changes during the exercise test as well as those with congestive heart failure, ejection fraction <50%, and cardiac transplant patients. Patients tested from 1996 to 2001 (n=462) were used to develop separate equations for those who were and were not on β-blocker therapy, whereas those tested between May 2001 and April 2002 (n=94) were used as a cross-validation sample for the β-blocker specific formula. Linear regression analysis generated the following equations: for non-β-blocked patients, HR_{max} = 200 - 0.9 × age; and for β-blocked patients, HR_{max} = 164 - 0.7 × age. There was a standard error of estimate of 18 beats/min for the latter equation. Among the cross-validation group of β-blocked patients, mean predicted HR_{max} was not significantly different from the mean measured HR_{max}, indicating good validity of the newly developed equation. While the mean error of prediction of this equation is low (-0.4±19 beats/min), there is still significant individual variability in HR_{max} that must be considered when applying this equation. While there have been at least 8 HR_{max} prediction equations developed since the 1970s, the equation generated by Brawner and colleagues, is the first to be developed specifically in a wide age-range of patients (40 to 80 years) with coronary heart disease and on β-blocker therapy. It is important to have a valid equation in this population, as these individuals are commonly referred for exercise stress testing as well as for rehabilitative exercise therapy. The use of this equation will result in more appropriate exercise test termination criteria as well as a more accurate prescription of exercise intensity for this subset of patients. However, the authors point out that despite the improved predictive accuracy of this equation compared with earlier equations, there is still substantial individual variability in HR_{max}. Consequently, whenever possible, it is still recommended to conduct a maximal effort exercise stress test in order to determine the individual's exact HR_{max}. When a maximal exercise stress test is not an option, using the authors' equation will provide the most accurate prediction of HR_{max} in coronary heart disease patients taking β-blockers.
Effect of endurance training on the determinants of peak exercise oxygen consumption in elderly patients with stable compensated heart failure and preserved ejection fraction

M. J. Haykowsky, P. H. Brubaker, K. P. Stewart, T. M. Morgan, J. Eggebeen, D. W. Kitzman

J Am Coll Cardiol. 2012;60:120-128

Heart failure with preserved ejection fraction (HFPEF) is the most common form of heart failure in older persons, it is increasing in prevalence, outcomes are poor, and there have been no effective drug treatments described to date. Kitzman et al were the first to report in 2010 that aerobic exercise training improved exercise capacity (VO_{2peak}) and quality of life in elderly persons with HFPEF. That finding was subsequently reproduced by others. In an earlier work, Haykowsky and Kitzman collaborated to examine the determinants of the severely reduced VO_{2peak} in elderly patients with HFPEF. They studied 44 HFPEF patients and 24 healthy age-matched subjects. They found that, contrary to a prior report from their group in a smaller group of patients, left ventricular end diastolic volume and stroke volume in HFPEF were not different from normal subjects. They found that the lower cardiac output at peak exercise in HFPEF was due entirely to reduced peak exercise heart rate. This phenomenon of relative chronotropic incompetence had been reported previously by their group and reproduced by Borlaug and colleagues. The lower cardiac output at peak exercise accounted for about 50% of the lower VO_{2peak} in HFPEF compared to healthy older persons. The authors also found that the other 50% were accounted for by reduced peak arteriovenous oxygen difference, representing peripheral, noncardiac factors.

In their follow-up study, the investigators sought to understand the determinants of the improvement in VO_{2} that had been observed in the 2010 report in HFPEF patients. They used similar methods to assess left ventricular volume response, calculate arteriovenous oxygen difference, and determine heart rate by means of the ECG. They found that the peak heart rate response to exercise improved by exercise training in elderly HFPEF patients, but that the increase was almost completely counterbalanced by a lower stroke volume response to exercise. Thus, cardiac output did not change significantly with training. As a result, essentially all of the training-related improvement in VO_{2} was associated with improvement in peak arteriovenous oxygen difference, involving peripheral factors such as improved arterial or skeletal muscle function.

A subsequent study indicated that exercise training did not improve arterial stiffness or dilation, thus implicating reduced skeletal muscle function as a key determinant of the improvement in VO_{2} following exercise training in older HFPEF patients. Improvement in chronotropic responsiveness with training in chronic heart failure has also been described in patients with HF and reduced EF.

Chinese author Mo Yan, who wrote his first books as a PLA soldier, receives the Nobel Prize in Literature; the Shard, Europe’s tallest building, is opened in London; and Kim Jong-un is appointed the Supreme Leader of North Korea
Cardiopulmonary exercise (CPX) testing is an important noninvasive method that can add significantly to diagnosis and prognosis of a wide variety of cardiovascular disorders. It is relatively inexpensive to perform, the equipment is widely available commercially, and compared with most other diagnostic testing equipment, is relatively inexpensive. However, CPX testing is woefully underused, perhaps because, even though the concepts are simple, they are not familiar. Other than for research and heart failure/transplant, cardiology physicians are usually not experienced in the technique.

This consensus document led by Guazzi and colleagues represents an effort to standardize, simplify, and clarify the role of CPX in a variety of cardiovascular disorders. The lead authors gained the support of major cardiovascular societies, assembled a group of experts from North America and Europe, and helped lead the group to consensus on a variety of issues. They then led the development of what is an extremely lucid, yet detailed report. The document is well laid out and easy-to-use. The specific parameters and guidelines for testing of each condition are given along with rationale. There are a number of tables that help to familiarize clinicians with the measurements that can be gained from CPX and how they are used for each condition.

The document has been endorsed by the key cardiovascular professional societies and published in their journals in the US and Europe. The work represents a handy, useful, and clinically relevant guide.
Resting heart rate and heart rate reserve in advanced heart failure have distinct pathophysiologic correlates and prognostic impact: a prospective pilot study

J. Benes, M. Kotrc, B. A. Borlaug, K. Lefflerova, P. Jarolim, B. Bendlova, A. Jabor, J. Kautzner, V. Melenovsky

JACC Heart Failure. 2013;1(3):259-266

A hallmark characteristic of chronic heart failure (HF), associated with either a reduced (HFREF) or preserved ejection fraction (HFPEF), is a markedly reduced capacity for physical exertion. This is perceived subjectively as exertional dyspnea and fatigue that impairs quality of life, is measured objectively by VO2peak, and is large. Often underappreciated, is that peak heart rate (HR) is usually significantly reduced and is an independent contributor to reduced VO2peak. The reduction in peak HR may appear relatively mild, but in the context of reduced stroke volume it represents a major deficit. In addition, even when the peak HR is only mildly reduced, HR reserve (ie, degree of heart rate augmentation above resting levels) is often substantially reduced. The impact of the reduced chronotropic response is magnified in older persons who already have underlying age-related reduced peak HR.

The impaired chronotropic response in HF patients has important implications for function, quality of life, and prognosis. It also has therapeutic implications since reversing such a deficit would represent a rather large, clinically meaningful effect size. Chronotropic index is predictive of events, even with high rate of β-blocker treatment.

The report from Benes and colleagues helps elucidate both the pathophysiology and prognostic significance of abnormal chronotropic responses in chronic HF. They describe a novel method, biomarker profiling, and partitioning of the components of chronotropic incompetence (CI) and a group of healthy controls. They compared the prognostic impact and biomarker correlates of both resting HR and CI in 81 patients with advanced HFREF with 25 age-, sex-, and size-matched healthy controls.

The report highlights the prevalence of CI in the HF population. Two-thirds of the HF patients met formal criteria for CI, within the range (20% to 70%) reported in the HF literature. Benes and colleagues used failure to obtain ≥80% of the HR reserve during a graded exercise test as the primary criteria for CI—a reasonable and practical definition. Benes and colleagues used biomarker/neurohormonal profiling to examine potential mechanisms in HF. This rests on the assumption that individual biomarkers and neurohormones are triggered by a variety of specific conditions, and that they can be grouped in clusters according to their clinical and mechanistic inferences, including increased myocardial stress, inflammation, myocyte injury, and neuroendocrine response to HF.

Resting HR correlated with myocardial stress and inflammation, while HR reserve correlated with neurohormonal activation. In healthy controls, the HR reserve was highly correlated with the increase in plasma norepinephrine, but this relationship was uncoupled in HF patients, suggesting diminished sinus node responsiveness in the latter group. This is similar to Samejima and colleagues who demonstrated that the ratio of change in HR to change in log of norepinephrine, an index of sinoatrial node sympathetic responsiveness, decreased progressively with the severity of HF.

An important finding of the investigation by Benes and colleagues was the prognostic impact of resting HR and HR reserve. Over a follow-up of 468 days, 35% of patients had an adverse event. Patients with a low resting HR (≤67 beats/min) had a lower risk of adverse outcomes compared with those in the upper quartile of resting HR. In contrast, patients in the lowest quartile of HR reserve displayed increased risk of adverse outcomes. The patients with the highest risk were those in whom both parameters were abnormal. Thus, a high resting HR combined with a low HR reserve portended the worst prognosis for advanced HFREF patients.

Juventus F.C. wins the 29th Series A football title; a new species of theropod dinosaur, Aorun zhaoi, dating from 161 million years ago, is discovered in China; and flash floods and landslides in Uttarakhand and Himachal Pradesh in India kill more than 1000 persons...
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