

Heart rate score, a measure related to chronotropic incompetence in pacemaker patients



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BACKGROUND Heart rate score (HrSc) $\geq 70\%$ in cardiac resynchronization therapy defibrillator and implantable cardioverter-defibrillator subjects predicts 5-year mortality risk. A high HrSc suggests few sensed cardiac cycles above the programmed lower rate.

OBJECTIVE To determine if HrSc is related to chronotropic incompetence (CI) in pacemaker (PM) subjects.

METHODS HrSc is the percentage of all atrial-paced and sensed events in the single tallest 10 beats/min histogram bin programmed to DDD 60/min. The prospective LIFE study of PM subjects examined multiple treadmill-based measures of CI. The 1-month postimplant DDD 60/min PM rate histogram prior to treadmill was retrospectively analyzed for HrSc. Measures of CI were applied to submaximal treadmill data in the DDD mode. HrSc was compared to these CI measures and to clinical indications for PM.

RESULTS The 1-month histogram demonstrated HrSc $\geq 70\%$ in 43% of subjects. HrSc $\geq 70\%$ correlated with a clinical diagnosis of sick

sinus syndrome ($P < .001$). CI was present in 34%–88% of subjects by treadmill-based measures. Agreement between treadmill-based measures for CI was poor and varied from 39% to 83%. HrSc $\geq 70\%$, as a measure of CI, was most highly correlated with unpaced heart rate $< 70\%$ of age-predicted maximum heart rate (67%) (odds ratio 3.7, $P < .001$).

CONCLUSIONS HrSc $\geq 70\%$ correlates with treadmill measures of CI and clinical sick sinus syndrome. HrSc $\geq 70\%$ is a measure of CI in PM subjects that is inexpensive, repeatable, and quantitative.

KEYWORDS Chronotropic incompetence; Heart rate score; Pacemaker; Risk assessment; Treadmill testing

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Introduction

Heart rate score (HrSc) is a recently described machine learning–derived parameter of long-term heart rate variation. It is defined as the percentage of all atrial-paced and sensed events in the single tallest 10 beats/min device histogram bin.¹ Subjects receiving an implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy defibrillator (CRT-D) with an earliest postimplant HrSc $\geq 70\%$ were at greatest risk of all-cause mortality over the next 5 years.^{1,2} Dual sensor–based pacing lowered HrSc by a greater amount than single-sensor rate-responsive pacing,³ with an associated increase in pacing rate. The underlying mechanisms contributing to the prognostic value of HrSc are unknown, but chronotropic incompetence (CI) is one proposed mechanism suggested by the relationship of HrSc to rate-responsive pacing, and the HrSc parameter being defined by the rate histogram.

We hypothesized that HrSc may correlate with CI in pacemaker (PM) subjects. The “Limiting chronotropic

incompetence in pacemaker recipients” (LIFE) study is one of only a few prior studies that compared multiple treadmill-based measures of CI.⁴ The deidentified data from the LIFE study was reassessed first to determine the relationship between HrSc and the clinical indication for PM implantation, and secondly to assess the relationship of an abnormal HrSc $\geq 70\%$ to treadmill-based measures of CI.

Methods

This study is a retrospective analysis of deidentified data from the LIFE clinical study published in 2008 and owned by Boston Scientific (Marlboro, MA). The LIFE study enrolled 1566 subjects after informed consent. The trial met requirements of the Declaration of Helsinki (2000). The research was carried out prior to 2008 at a time when there was no requirement for trial registration. All subjects met clinical indications for an implantable PM and underwent implantation of an Insignia Plus or Ultra dual-chamber PM (Boston Scientific, Marlboro, MA). Two of the indications listed in the LIFE study, sick sinus syndrome and sinus bradycardia, were grouped together as sick sinus syndrome for most of this analysis, as they both pertain to

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KEY FINDINGS

- The heart rate score is the percentage of all atrial-paced and sensed events in the single tallest 10 beats/min histogram bin programmed to DDD 60/min.
- Heart rate score $\geq 70\%$ correlates with a clinical diagnosis of sick sinus syndrome and treadmill peak heart rate $< 70\%$ and $< 85\%$ of age-predicted maximum heart rate, which are measures of chronotropic incompetence.
- Heart Rate Score is a simple, inexpensive, and quantitative method to follow chronotropic incompetence in subjects with CIEDs.

CI. At 1 month postimplant, subjects were to undergo submaximal exercise treadmill testing in the DDD-60 mode to assess the spontaneous rhythm that could indicate chronotropic incompetence. The 4 measures of CI based on treadmill testing in the LIFE study⁴ were based on heart rate reserve (HRR), age-predicted maximum heart rate (APMHR), and metabolic chronotropic reserve (MCR) slope:

- (1) $< 80\%$ HRR = $\text{Max HRR} < 0.80 \text{ HRR}$, $\text{HRR} = \text{Max HR} - \text{Rest HR}$
- (2) $< 85\%$ APMHR = $\text{Max HR} < 0.85 \times \text{APMHR}$
- (3) $< 70\%$ APMHR = $\text{Max HR} \leq 0.7 \times \text{APMHR}$
- (4) MCR slope (LIFE definition) = slope of HRR to metabolic reserve plotted at each stage (MCR slope < 0.8 determined by the Wilkoff method^{5,6})

The Chronotropic Assessment Exercise Protocol is a symptom-limited exercise test that increases treadmill speed and grade in 2-minute intervals. Subjects had to complete ≥ 3 stages of a Chronotropic Assessment Exercise Protocol and reached a Borg exertional scale ≥ 16 for level of peak perceived exertion in order to be included in the MCR slope calculation. Thus, there are fewer subjects meeting this measure. The MCR slope method defines CI by a slope of < 0.8 . Slope is calculated by the ratio of % HRR used to % metabolic reserve used at each exercise stage, and has been described in detail elsewhere.^{5,6}

In the LIFE study, all subjects were programmed to DDD pacing mode with lower rate limit (LRL) of 60 (DDD-60) for the first month and for the treadmill study. Thus, the treadmill and the histogram were recorded with the LRL programmed to 60 and no rate-responsive pacing to make comparisons possible. As a result, any atrial cycles at rates > 60 had to be a spontaneous rhythm. The HrSc was measured from the pacemaker interrogation at 1 month postimplantation, but prior to the treadmill testing when available. The HrSc was defined as the height of the tallest 10 beats/min histogram bin for combined atrial sensed and paced events, expressed as a percentage of all atrial events (Figure 1). The rate histogram used in this analysis was the long-term histogram,

which is different from the short-term beat-to-beat rate plots available for many devices.

Statistical methods

Continuous variables are presented as mean \pm standard deviation and categorical variables are presented as number (%) of subjects meeting specified criteria, unless otherwise noted. Group comparisons were performed using F-tests for continuous variables and Pearson χ^2 tests for categorical variables. Pairwise comparisons of the different measures of chronotropic response in the LIFE study were evaluated using agreement and Cohen Kappa coefficient. Agreement was defined as the percentage of concordant classifications out of the total number of classifications ($[\text{CI for both measures} + \text{chronotropic competence (CC) for both measures}] / [\text{total measures}]$). Evaluations of the association of HrSc $\geq 70\%$ with various measures of chronotropic response in the LIFE study were performed using logistic regression modeling, in which the classification of CI was the dependent variable and HrSc ($\geq 70\%$ vs $< 70\%$) was the independent variable. One of these models utilized all classifications of CI within a subject, allowing for multiple observations per patient; repeated measures logistic regression with a compound symmetry correlation structure was performed to account for the within-patient correlation. SAS version 9.4 (SAS Institute, Cary, NC) was used for all statistical analyses.

Results

Patient flow

The LIFE study enrolled 1566 subjects, of which 1538 had pacemaker implantation. Of these subjects, there was no 1-month follow-up treadmill completed or data were missing in a total of 290 subjects (Figure 2A), leaving 1258 subjects. One-month digital PM interrogation data were available for analysis of HrSc data in 501 subjects, but 18 of these subjects did not have treadmill testing. The detailed numbers for each test are shown in a Venn diagram (Figure 2B). The CI tests $< 80\%$ HRR, $< 70\%$ APMHR, and $< 85\%$ APMHR of predicted maximum were recorded in 1096 treadmill tests. The more complex MCR slope < 0.8 , which required at least 3 stages to be completed, was available in 547 subjects, and HrSc was available in 483 subjects who had treadmill testing.

Demographic data

Age, sex, body mass index, systolic blood pressure, diastolic blood pressure, NYHA heart failure (HF) functional class,⁷ and pacemaker indication were examined in several groups of subjects that comprised the 1538 with PM implant. All CI tests were available in 149 subjects; some CI tests were available in 1127 subjects; and no CI tests were available in 262 subjects ($149 + 1127 + 262 = 1538$). There were no statistically significant differences in demographics between these 3 groups to suggest selective sampling.

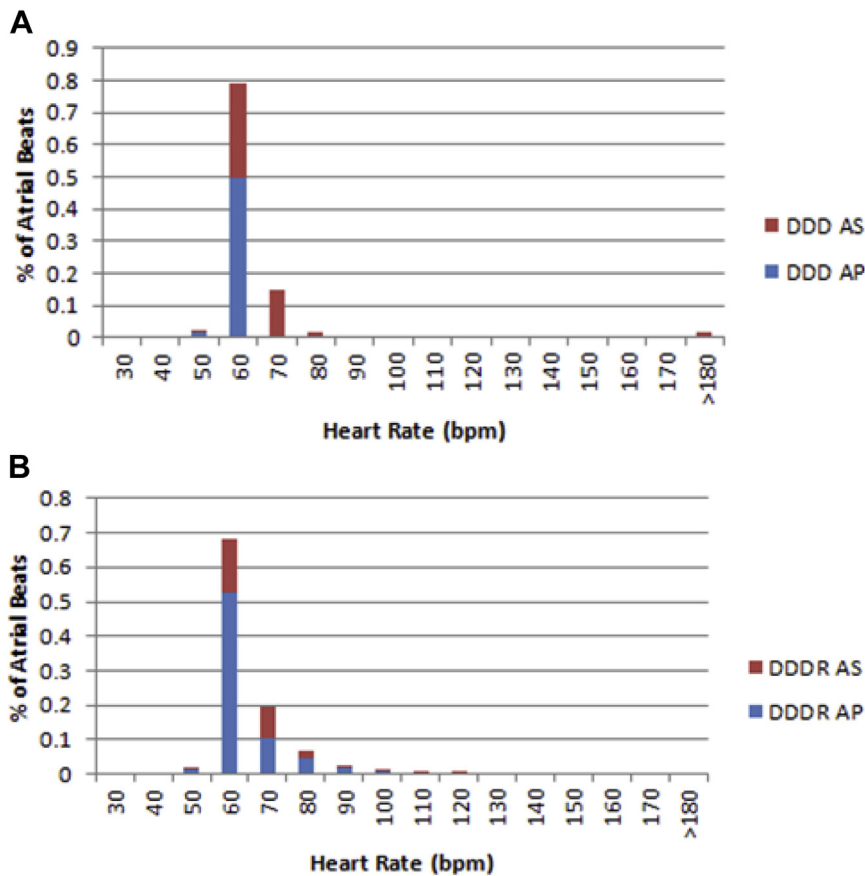


Figure 1 Heart rate score (HrSc) from a patient in the LIFE trial. **A:** The baseline atrial sensed (AS) and atrial paced (AP) histogram in DDD mode with lower rate limit 60/min. HrSc = 79% and is the height of the tallest bin, which is commonly the lowest rate bin. **B:** The same patient programmed later to DDDR mode 60–120 after 30 days follow-up. The atrial sensed beats above rate 60 remains similar to panel A, but the atrial beats paced above 60 increase in panel B because of the rate-responsive pacing. The HrSc in DDDR pacing in panel B is lowered to 68% in the tallest bin, which is still the lowest rate bin. The data in both panels include 30 days outpatient recording and do not include treadmill testing.

Correlation of heart rate score with clinical diagnosis

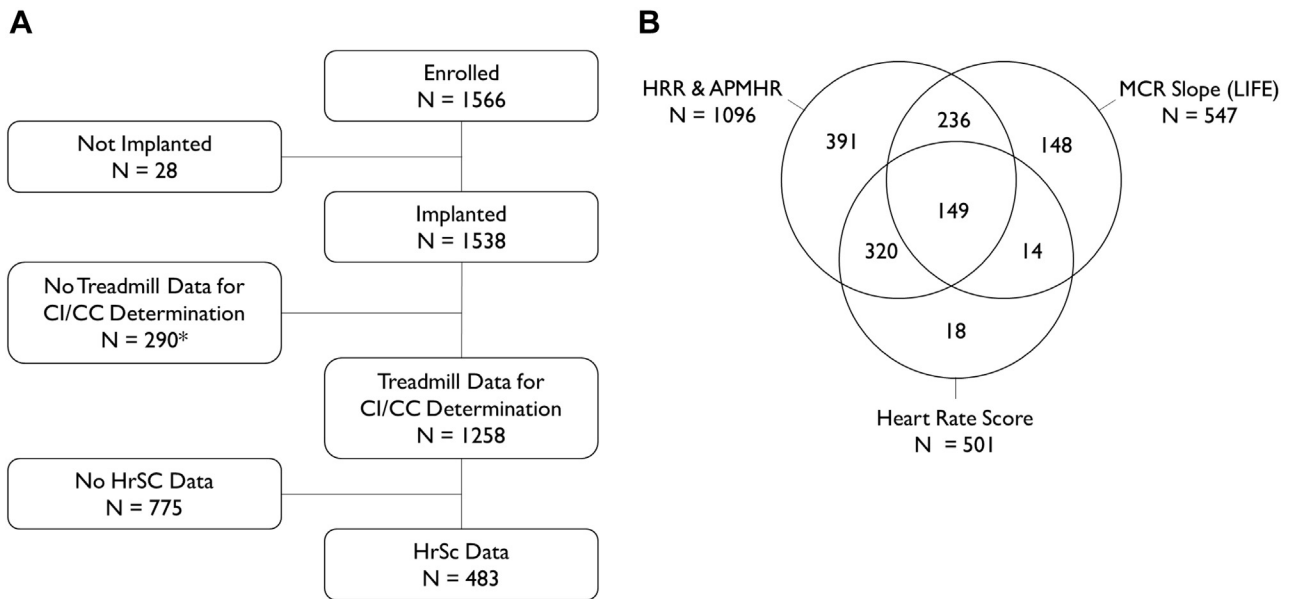
The demographics for LIFE study subjects with HrSc available are shown in Table 1 (n = 501), and are grouped by HrSc (low <30%, medium 30%–69%, high \geq 70% as in prior publications¹). Low HrSc subjects (HrSc <30%) tended to be younger. The indication for all pacemakers listed by the LIFE investigators was sinus node disease (sick sinus syndrome and sinus bradycardia) in 58% and atrioventricular conduction disease in 25%, with the remainder having both diagnoses. Subjects with HrSc \geq 70% (n = 214) more likely had a clinical diagnosis of sick sinus syndrome (76.2%) than subjects with HrSc <30% or mid-range HrSc 30%–69% ($P < .001$). Subjects with HrSc \geq 70% were less likely to have atrioventricular conduction disorders (14%) (Table 1). This is consistent with subjects with high HrSc having less spontaneous heart rates above the LRL of 60/min.

Baseline heart rate score compared to 4 treadmill-based measures of chronotropic incompetence

The rates of CI for each of the 4 treadmill-based measures and HrSc \geq 70% are shown in Figure 3A. CI rates across the

5 measures ranged from 34% (LIFE-MCR slope <0.8) to 88% ($<80\%$ HRR). Agreement of chronotropic response classification, including both CC and CI, between each pairwise comparison of the measures is shown in Figure 3B. Conventional measures of CI ($<80\%$ HRR, peak HR $<85\%$ APMHR, peak HR $<70\%$ APMHR, and LIFE definition of CI) have a wide range of agreement with each other (39%–83% agreement in CI and CC classifications) (Figure 2B). HrSc \geq 70% as a measure of CI correlated with age-predicted maximum heart rate CI measures (peak heart rate $<70\%$ APMHR and $<85\%$ APMHR; $P < .001$ for both) (Table 2). The $<80\%$ HRR ($P = .3$) and MCR slope <0.8 ($P = .5$) were not individually correlated with HrSc $>70\%$ as measures of CI (Table 2 and Figure 3B). A repeated measures logistic regression model utilizing all available CI classifications indicated that those considered to have CI by any of the CI treadmill measures were collectively more likely to have an HrSc \geq 70% (odds ratio: 2.0, 95% confidence interval: 1.5–2.6, $P < .001$; Table 2).

The distributions of baseline HrSc for the subsequent 4 treadmill-based CI measures are shown in Figure 4 for patients deemed to have CI by that measure in blue and CC in red. Across all 4 treadmill-based measures of CI, subjects



*There were 18 subjects with HrSc data but no treadmill data

Figure 2 Patients and data flow in the LIFE study. **A:** Flowchart. **B:** Three-way Venn diagram of data availability. A total of 1258 patients had treadmill data available for determination of at least 1 chronotropic incompetence (CI) measure, of which 483 had DDD histogram data available for calculation of heart rate score (HrSc). There were 149 patients with available data on all 4 CI measures and HrSc. APMHR = age-predicted maximum heart rate; CC = chronotropic competence; HRR = heart rate reserve; MCR = metabolic chronotropic reserve.

otherwise defined as having CI had higher HrSc (Figure 4). In contrast, those subjects classified as CC had a broad distribution of HrSc and 3 of the 4 measures of CI had a small peak at HrSc 30%–39% among CC subjects. This is consistent with spontaneous sinus rhythm above the LRL of 60. The strongest association between CI and HrSc $\geq 70\%$ was observed with the CI definition of peak treadmill heart rate $< 70\%$ of APMHR (odds ratio 3.7, $P < .001$; Table 2). This association can be seen in Figure 4C, in which the CI patients were more likely to have HrSc $\geq 70\%$ and the CC patients more likely to

have HrSc $< 70\%$. A weaker, but still significant, association was observed between HrSc $\geq 70\%$ and CI defined by peak treadmill heart rate $< 85\%$ of APMHR (Table 2 and Figure 4B).

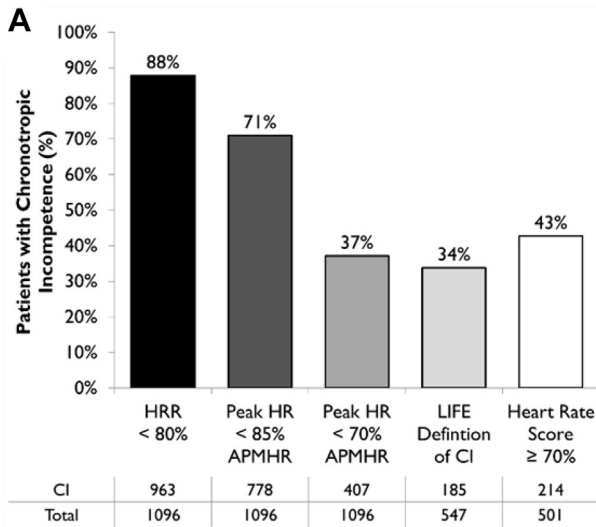
Discussion

Pacemaker and defibrillator subjects who have little or no spontaneous heart rates above the programmed LRL, as seen on the device histogram, have a high HrSc $> 70\%$.

Table 1 LIFE study subjects with heart rate score data available (n = 501); baseline demographic data presented for each group, with statistical differences by analysis of variance

Variable	Statistic	HrSc Group			P value
		$< 30\%$ (n = 39)	30%–69% (n = 248)	$\geq 70\%$ (n = 214)	
Age	Mean \pm SD	64 \pm 13	72 \pm 11	73 \pm 10	$< .001$
Sex	Female (%)	28.2%	41.9%	39.3%	.26
BMI	Mean \pm SD	28.6 \pm 6.6	27.9 \pm 6.0	28.0 \pm 5.0	.76
BP systolic	Mean \pm SD	134 \pm 22	140 \pm 23	143 \pm 25	.09
BP diastolic	Mean \pm SD	73 \pm 13	72 \pm 13	71 \pm 13	.41
NYHA HF functional class	Class I (%)	41.0%	37.1%	40.2%	.12
	Class II (%)	0.0%	6.9%	10.3%	
	Class III (%)	2.6%	0.4%	0.5%	
	Class IV (%)	7.7%	9.3%	12.6%	
	None (%)	48.7%	46.4%	36.5%	
Indication for pacemaker implant	Sick sinus syndrome (%)	30.8%	32.3%	46.3%	$< .001$
	Sinus bradycardia (%)	10.3%	13.7%	29.9%	
	Third-degree AV block (%)	28.2%	20.6%	7.9%	
	Second-degree AV block (%)	15.4%	17.7%	6.1%	

BMI = body mass index; BP = blood pressure; HF = heart failure; HrSc = heart rate score.



B Pairwise CR Classification

Upper half: Agreement N (%) | Lower half: Cohen's Kappa (P-value)

	HRR < 80%	Peak HR < 85% APMHR	Peak HR < 70% APMHR	LIFE Definition of CI	Heart Rate Score ≥ 70%
HRR < 80%	-	911/1096 (83%)	540/1096 (49%)	148/285 (39%)	215/469 (46%)
Peak HR < 85% APMHR	0.50 (< 0.001)	-	725/1096 (66%)	169/385 (44%)	254/469 (54%)
Peak HR < 70% APMHR	0.15 (< 0.001)	0.39 (< 0.001)	-	228/385 (59%)	313/469 (67%)
LIFE Definition of CI	0.01 (0.61)	-0.02 (0.69)	0.07 (0.20)	-	89/163 (55%)
Heart Rate Score ≥ 70%	0.03 (0.31)	0.14 (< 0.001)	0.31 (< 0.001)	0.06 (0.45)	-

Figure 3 A: Percentage of subjects in LIFE study meeting definitions for chronotropic incompetence (CI). B: Comparison of CI and chronotropic competence (CC) classifications between all pairwise combinations of definitions. Accuracy defined as all classifications that agreed across both measures (CC or CI) divided by all classifications. P value < .05 indicates significant concordance between measures. Heart rate score >70% correlates with <70% age-predicted maximum heart rate (APMHR) and <85% APMHR. HR = heart rate; HRR = heart rate reserve.

This led us to hypothesize that there is a relationship between HrSc and CI. The major observations of this analysis using the LIFE trial data are, first, that HrSc ≥70% is associated with the clinical diagnosis of sick sinus syndrome (P < .001) and thus, CI (Table 1); second, that HrSc ≥70% correlated with previously described treadmill-based definitions of CI, such as maximum heart rate on a standardized exercise test <70% of APMHR (P < .001) (Table 2)⁸⁻¹⁰; and furthermore, that any treadmill-based measure of CI is associated with HrSc ≥70%, supporting our hypothesis that HrSc ≥70% is a marker of CI.

The connection between HrSc and the maximum heart rate on a treadmill test may not be immediately clear. The

Table 2 Association of heart rate score ≥70% and various definitions of chronotropic incompetence

Definition of CI	OR	95%CI	P
<80% HRR	1.3	0.8-2.4	.307
<85% APMHR	2.2	1.4-3.4	<.001
<70% APMHR	3.7	2.5-5.5	<.001
LIFE definition of CI	1.3	0.7-2.4	.455
All definitions[†]	2.0	1.5-2.6	<.001

APMHR = age-predicted maximum heart rate; CI = chronotropic incompetence; HRR = heart rate reserve; OR = odds ratio; 95%CI = 95% confidence interval.

Odds ratio >1 indicates HrSc ≥70% associated with CI. Separate logistic regression models were evaluated for each definition of CI.

[†]Accounted for repeated measures within patient.

long-term rate histogram does not provide beat-to-beat heart rate variation in the plots and the HrSc does not reflect the peak heart rate on the treadmill test, as HrSc was measured before treadmill. HrSc does reflect the heart rate distribution during activities of daily living in the prior 30 days. The tallest rate histogram bin is almost always the lowest rate bin above the LRL of the pacemaker, 60 in this study (Figure 1). The HrSc is measured by the height of the tallest rate bin, which is usually not the highest rate bin, which is where the peak treadmill heart rate would be registered. However, there is a mathematical connection between the APMHR and the HrSc. The lower the APMHR, the less spontaneous variation in heart rate will occur above the LRL of 60/min with activities of daily living. Less heart rate increases will result in most of the heart beats being concentrated into fewer bins, resulting in a higher percentage of beats in the lowest bin (higher HrSc). Thus, there is an inverse relationship between APMHR and HrSc, with low APMHR associated with higher HrSc.

CI indicates an ineffective acceleration in heart rate to meet physiological demands. It refers to an impaired sinus rate with a mismatch of cardiac output for the patient's metabolic needs.⁸ CI may involve failure to achieve a certain percentage of age-predicted maximum heart rate in response to exercise,^{9,10} a sinus rate slower than expected during a portion of exercise,¹¹ and an abnormally slow rate of heart rate recovery post exercise.¹² CI can be associated with resting sinus bradycardia.^{13,14} Despite lack of a standard definition for identifying subjects with CI, CI has been associated with increased all-cause mortality¹⁵ and cardiovascular mortality in multiple studies,^{16,17} including the Framingham longitudinal follow-up.¹⁸

An association between CI and HF was recently reviewed.¹⁹ CI is a heterogeneous phenotypic diagnosis with multiple associated etiologic causes, such as HF and pharmacologic therapy.^{8,13} As there are multiple methods of assessment and detection of CI, the incidence, prevalence, and even definitions of CI vary widely. In a PM population the LIFE study definition yielded a CI prevalence of 34%.⁴ In contrast, in a chronic HF population, CI was observed in 66% of subjects, as defined by <80% of the HRR (% HRR).²⁰ The LIFE

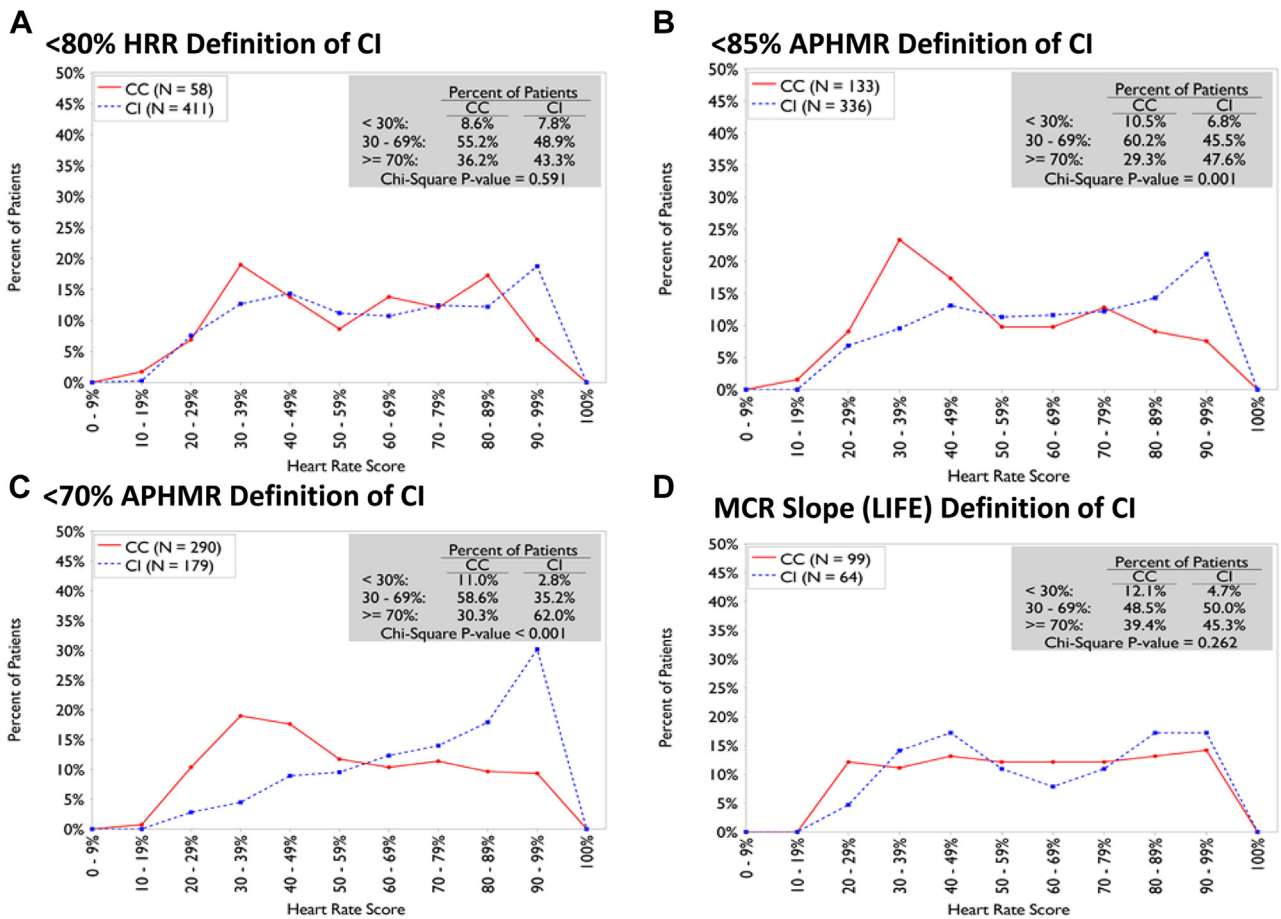


Figure 4 Baseline heart rate score (HrSc) profiles in DDD pacing mode for subjects in LIFE study with chronotropic competence (CC; in red) and chronotropic incompetence (CI; in blue) based on the subsequent 4 definitions of CI. **A:** <80% heart rate reserve definition of CI. CC and CI have similar distributions of HrSc. **B:** <85% age-predicted maximum heart rate (APHMR) definition of CI. CC and CI have different distributions of HrSc. **C:** <70% APHMR definition of CI. CC and CI have the greatest divergence of HrSc distribution. Subjects with CI have a distribution skewed towards high HrSc $\geq 70\%$ compared to subjects with CC most evident for <70% APHMR. **D:** Metabolic chronotropic reserve slope (LIFE) definition of CI. CC and CI have similar distributions of HrSc.

study did not document objective evidence of systolic and diastolic dysfunction, biomarker data, or HF etiology, and there was no HF drug control, and thus no conclusions regarding the association of CI and HF can be made based on this analysis.

Measures of CI described previously include a reduced MCR slope,¹⁷ achieving <70%–85% of APMHR on submaximal exercise testing,⁶ or reduction in age-predicted HRR.²¹ MCR slope, APMHR, and HRR require careful exercise testing. This is costly, is difficult to perform in subjects with physical limitations, and reflects variability of patient performance at one point in time. In addition, none of these treadmill-based measures has emerged as the clear gold standard for CI management. HrSc $\geq 70\%$ can be measured repeatedly and remotely from a PM interrogation, is low cost, is quantitative, and is an alternative measure of CI that correlates with APMHR and a clinical diagnosis of sick sinus syndrome. Future prospective validation is required to determine the utility of HrSc as a diagnostic tool for CI. It also needs to be determined if HrSc measurement can be extended to wearable monitors.

Prior studies using a large database of ICD and CRT-D subjects have shown that an early postimplant HrSc $\geq 70\%$ predicts higher mortality in subjects over a 5-year follow-up.¹ Furthermore, CRT-D subjects with baseline HrSc $\geq 70\%$ programmed to DDDR (vs DDD) in a propensity score-matched population have a better survival.² CI may also be associated with cardiovascular mortality.^{16–18} Accordingly, HrSc may be suitable for future investigations of the relationships between CI and survival in other device populations.

We have recently demonstrated that HrSc can be improved (reduced) and peak exercise rate increased by programming rate response with minute ventilation combined with accelerometer.³ A strategy of reducing HrSc and thus improving HrSc with sensor-driven programming could be tested prospectively and randomized in future outcomes trials. Rate-responsive pacing has shown to increase exercise times compared to fixed-rate pacing.²² However, simply programming faster pacing rates with more aggressive sensor response and higher maximal sensor rates may not be the best approach in all PM subjects. There is evidence that with pacing at faster rates there can be reductions in

myocardial performance in some subjects.²³ More recently, the myocardial force frequency relationship to pacing rate has been examined noninvasively in subjects with left ventricular systolic dysfunction.²⁴ Tailoring the maximal sensor rate to the critical rate, increased exercise time, and increased peak oxygen consumption but above a critical paced rate (mean 109 ppm, <70% APMHR) contractility was reduced. Thus, there is evidence that in the HF population with CI, care needs to be taken to not pace overly rapidly.

Limitations

This study is retrospective and hypothesis-generating. Therefore, there is a need to assess HrSc prospectively to identify PM subjects with CI and test for prospective outcomes. This study did not set out to examine which definition of CI is best. It is unclear what endpoints would be used and likely would require some long-term outcome measure to determine a “gold-standard test for CI.” However, this is not central to use of HrSc. The sensitivity and specificity of HrSc for identifying CI are not defined owing to lack of a gold standard. In this study, HrSc was measured by a PM and, therefore, conclusions about CI apply to that population. Lastly, this study was done entirely with the PM LRL of 60 ppm.

Conclusion

These data are the first to suggest that HrSc is associated with CI in a PM population. HrSc is also associated with the clinical diagnosis of sinus node dysfunction. HrSc correlates best with the established treadmill-based measure of CI exercise rate <70% APMHR. HrSc \geq 70% is common (43%) in the LIFE study PM population. This HrSc methodology can be used in most devices that have fixed bin widths on the rate histograms; and unlike other measures of CI, it does not require an exercise test, which adds cost and is affected by patient comorbidities. Correlation of HrSc with clinical and exercise test indicators of CI suggests that HrSc has the potential to become a measure for CI, to optimize rate-responsive pacing in PM subjects, and to remotely monitor worsening HF.

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Authorship

All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent

All patients enrolled in the LIFE study provided written informed consent.

Ethics Statement

The research reported in this paper adhered to the guidelines set forth by the Declaration of Helsinki. The LIFE study received institutional review board (IRB) approval of the protocol and ethics at each study center. IRB approval of the current study was waived due to the use of retrospective and deidentified data.

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