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EDITORIAL COMMENT

Are We Approaching Chronotropy (In)competently?*

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An appropriate chronotropic response is essential for increasing cardiac output (CO) in order to meet the body's metabolic needs during exertion. The relationship between heart rate (HR) and CO is mediated by stroke volume (SV) and summarized by the well-known equation: CO = HR × SV. In the setting of chronotropic incompetence, the HR response to exercise is impaired and so too is CO, resulting in symptoms of exertional intolerance. Quantitatively, chronotropic incompetence has been defined as the inability to reach a percentage (often 80% or 85%) of the age-predicted maximum HR, which is usually defined by the Astrand formula (220 − age). (1) Although it is used extensively throughout medicine and exercise physiology, the Astrand formula has not been rigorously derived or validated, and several prior studies have shown considerable error in estimation of maximal HR (2). Application of the Astrand formula for diagnosis of chronotropic incompetence among patients with heart failure (HF) is predicated on the questionable assumption that the optimal HR response to exercise does not vary based on the presence or absence of cardiovascular diseases.

The development of rate-responsive pacing algorithms, which augment HR in response to an increase in physical activity, provides important symptomatic benefits in patients with chronotropic incompetence and normal ventricular function. The effects among patients with HF have been mixed. Despite this, rate-responsive pacing is frequently used in patients with HF and apparent chronotropic incompetence, commonly with an upper sensor rate between 120 and 130 beats/min, as is commonly programmed for immediate usability by implantable device manufacturers.

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In this issue of *JACC: Heart Failure*, Gierula et al. (3) test the provocative hypothesis that a tailored approach to rate-response programming based upon detailed understanding of the relationship between an individual's HR and contractility can improve exercise tolerance. The authors hypothesized that it may be possible to define a "critical" HR at which the normally positive force-frequency relationship (relationship between HR and contractility) becomes negative and that by limiting rate-responsive pacing to this "critical HR," exercise capacity could be improved. The authors performed their study in 2 phases. First, the authors measured the force-frequency relationship in patients (cardiac resynchronization therapy [CRT] patients and non-CRT, control patients without HF) by using a standardized pacing protocol with serial echocardiography. Contractility was inferred based on the ratio of non-invasively measured systolic blood pressure divided by left ventricular (LV) end-systolic volume. Next, the authors performed a randomized crossover study in a subset of the HF patients from the first phase to assess whether exercise tolerance differed when CRT devices were programmed to conventional rate-response parameters versus a "tailored" mode where the maximum sensor rate did not exceed the "critical" HR at which the force-frequency relationship became negative.

In the first phase of the study, the authors observed that, with increasing HR, contractility

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increased for control patients up to an average "critical" HR of 126 ± 15 beats/min. In contrast, HF patients demonstrated a much flatter slope and an average "critical" HR of 103 ± 22 beats/min ($p = 0.0002$ for comparison). In the second phase of the study, the authors observed that a "tailored" approach to rate-responsive pacing resulted in a lower mean peak HR during exercise (109 beats/min [95% confidence interval (CI)]: 106 to 112 beats/min vs. 138 beats/min [95% CI: 109 to 167 beats/min], respectively; $p < 0.0001$) and significant improvements in exercise time (475 vs. 425 s, respectively; $p = 0.0025$), peak V_{O_2} (17.3 vs. 16.6 ml/kg/min, respectively; $p = 0.0134$), O_2 pulse (13.4 vs. 10.2, respectively; $p < 0.0001$), and $V_E V_{CO_2}$ slope (31.8 vs. 33.7, respectively; $p = 0.0139$). From a physiological perspective, these findings support the hypothesis that, among patients with HF, there is a critical HR threshold after which ventricular function decreases. Strikingly, current data suggest that this critical threshold may often be well below both the maximum HR predicted by the Astrand formula HR and the accepted definitions of chronotropic incompetence. As a point of reference, for a 74-year-old patient with HF (mean age of the participant in the second phase), the maximum HR predicted by the Astrand formula would be 146 beats/min, and a diagnosis of chronotropic incompetence would be given with a maximum achieved HR of 117 beats/min during exercise testing, yet the mean "critical" HR threshold in this study was approximately 100 beats/min.

Although the use of a tailored approach to rate-response programming demonstrated a statistically significant benefit, it is important to understand whether the differences are likely to be clinically significant. The change in peak V_{O_2} observed in patients assigned to the "tailored" approach (0.7 ml/kg/min) in this study was identical to the improvement in peak V_{O_2} among patients with HF randomized to exercise training in the HF-ACTION study (4). In that study, the 0.7 ml/kg/min improvement in peak V_{O_2} was not associated with an improvement in the primary endpoint of mortality or HF hospitalization in unadjusted analyses. A 10% or 2.5 ml/kg/min improvement in peak V_{O_2} is customarily used as a clinically relevant change in peak V_{O_2} and is necessary to achieve a meaningful improvement in HF-related quality of life (4,5). However, if a "tailored" approach to rate-responsive programming were able to facilitate sustained increases in physical activity with salutary improvements on overall cardiovascular fitness, the long-term benefits of tailored programming combined with exercise training could be additive. A prospective, blinded, randomized clinical trial of a "tailored" programming approach coupled with exercise training is necessary to make that determination.

Although this study makes an important contribution to understanding optimal treatment of chronotropic incompetence in HF patients, several issues should be mentioned. First, the authors measured contractility indirectly by using systolic blood pressure divided by the LV end-systolic volume but did not prove that this measurement was optimal for defining the "critical" HR. Importantly, use of this measurement neglects the fact that HR-dependent changes in diastolic function may have profound impact on CO levels at higher HRs. A deeper understanding of the relationship between HR and diastolic function in this study is important for understanding the physiological impact of the study intervention and to understand whether this approach could be generalized to patients with HF with preserved ejection fraction. An echocardiographic measurement of both systolic and diastolic functions such as stroke volume may be superior to a surrogate of contractility for understanding an individual patient's "critical" HR. Second, based on the nature of the study, it is not possible to determine whether the exercise improvements observed in this study would demonstrate long-term durability or result in meaningful improvements in quality of life or overall health status. Third, the protocol required to determine the "critical" HR was resource intensive with a total testing time of approximately 40 min. Adoption of a validated formula to predict "critical" HR in patients with HF, followed by a "tailored" approach for patients with poor exercise tolerance, may provide population-level improvements in exercise capacity compared to the current immediately useful rate-response programming based on the Astrand formula. Fourth, the authors reported that rate-responsive pacing was necessary to achieve "critical" HR of 101 ± 19 beats/min in 47 of 52 patients (90%) who participated in the randomized-controlled crossover trial portion of the study. Although chronotropic incompetence is common in our practice, it is relatively uncommon to see such an extreme degree of chronotropic incompetence; this raises questions about generalizability of results and appropriate selection of patients for this type of intervention. Fifth, it is unclear whether the "critical" HR will vary based on loading conditions and dynamic changes in LV function, which is common after CRT. Finally, an important unanswered question is whether or not some degree of chronotropic incompetence should be considered an adaptive response to a failing heart that is unable to sustain an adequate CO level at higher HRs.

Gierula et al. (3) should be congratulated on an innovative and thought-provoking study that could represent an important step toward an improved understanding of the treatment of chronotropic incompetence in patients with HF. However, it should be emphasized that optimized rate-response parameters alone are unlikely to result in maximal patient benefit. As such, optimal rate response programming should be viewed as one component of a comprehensive strategy that includes optimization of atrioventricular timing, routine assessment and optimization of CRT pacing percentage, and exercise training for improving exercise tolerance in patients with HF.

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REFERENCES

1. Brubaker PH, Kitzman DW. Chronotropic incompetence: causes, consequences, and management. Circulation 2011;123:1010–20.

2. Roberts RA, Landwehr R. The surprising history of the "HRmax = 220-age" equation. J Exerc Physiol Online 2002;5.

3. Gierula J, Paton MF, Lowry JE, et al. Rate-response programming tailored to the force-frequency relationship improves exercise tolerance in chronic heart failure. J Am Coll Cardiol HF 2018;6:105–13.

4. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009;301:1439–50.

5. Flynn KE, Lin L, Moe GW, et al. Relationships between changes in patient-reported health status and functional capacity in outpatients with heart failure. Am Heart J 2012;163:88–94.

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