A hallmark characteristic of chronic heart failure (HF), associated with either a reduced ejection fraction (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 peak oxygen consumption (VO2), and is quantitatively large, with peakVO2 that is 15% to 40% below that of age-matched control subjects (1). Despite considerable efforts, the mechanisms of exercise intolerance in HF are incompletely understood, but understanding and manipulating them clearly holds the potential for significantly improving quality of life in these patients.

The impaired chronotropic response in HF patients has important implications for function, quality of life, and prognosis. It also has therapeutic implications because reversing such a deficit would represent a rather large, clinically meaningful effect size. In fact, we have reported that ~20% to 25% of these older HF patients meet formal criteria for chronotropic incompetence (CI) (9). Borlaug et al. (11) also reported that older HFpEF patients had a slower HR rise, lower peak exercise HR, and impaired HR recovery, all of which are indicative of abnormal autonomic function. Girotra et al. (12) showed that chronotropy is so strongly prognostic that even the HR response to a timed walk is predictive of events in older persons in the community. Furthermore, Dobre et al. (13) showed that chronotropic index was predictive of events in HF even in a population with a very high rate of beta-blocker usage.

In the context of reduced exercise capacity, the impaired chronotropic response in HF patients has important implications for function, quality of life, and prognosis. However, there has not been more interest in the chronotropic response in a patient population where exercise intolerance is so problematic. The impact of the reduced chronotropic response is magnified in older persons, who compose the majority of HF patients and who already have, as underlying normal age-related changes, reduced peak HR response. We demonstrated, in a group of 102 elderly patients with either HFrEF or HFpEF, that HR reserve was significantly correlated (r = 0.40) with peakVO2 (9). Moreover, these findings indicated that the increase in HR during exercise accounted for an appreciable portion of the observed differences in peakVO2 in these older HF patients. In a patient population with an average peakVO2 of 14 ml·kg⁻¹·min⁻¹, abnormal HR during exertion accounted for about 2 ml·kg⁻¹·min⁻¹ of peakVO2.

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Despite these reports and others that have confirmed the presence and importance of this phenomenon in HF, chronotropy remains the “Cinderella” of HF pathophysiology and management. It is underappreciated, overlooked, and waiting to be recognized for the gem that it is. The underappreciation of CI may be due partly due to multiple definitions of CI, the confounding effects of aging and
medications, and a remarkably limited understanding of the fundamental mechanism(s) responsible for this disorder. It is in regard to the mechanisms that the present report from Benes et al. (14) represents an important advance. The work helps elucidate both the pathophysiology and prognostic significance of abnormal chronotropic responses in chronic HF. This highly experienced team of investigators designed and conducted an elegant study using a relatively novel method, biomarker profiling, and partitioning of the components of CI and a group of healthy control subjects.

The investigators 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 control subjects (14). The well-matched control group is a particular strength of this study. A contemporaneous, appropriate, normative control group is critical for ensuring validity of conclusions in cross-sectional mechanistic studies.

This 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 (9), but is within the wide range (20% to 70%) reported in the HF literature (15–17). The substantial variability in reported CI prevalence in HF is likely influenced by the criteria employed to determine CI as well as differing patient characteristics (age, disease severity, type/dose medications). The majority of studies in the literature, including the investigation by Benes et al. (14), have used failure to obtain ≥80% of the HR reserve, obtained during a graded exercise test, as the primary criteria for CI, and we agree this is a reasonable, practical definition.

A particularly novel and creative aspect of the investigation by Benes et al. (14) was the use of biomarker/neurohormonal profiling. This is a novel, creative technique to noninvasively examine potential mechanisms in HF. It rests on the well-grounded assumption that elaboration of individual biomarkers and neurohormones are triggered by a variety of conditions, and that they can be grouped in clusters according to their clinical and mechanistic inferences, including: increased myocardial stress; inflammation; myocardial injury; and neuroendocrine response to HF. Benes et al. (14) wisely chose to partition the components of CI (resting HR and HR reserve) and to examine their individual profiles, which enhanced their mechanistic insights. Surprisingly, the resting HR and HR reserve were not intercorrelated and also associated with distinct biomarker profiles, suggesting that these 2 measures, previously thought to be tightly interconnected, have different mechanisms/pathophysiology. Resting HR correlated with myocardial stress and inflammation, whereas HR reserve correlated with neurohormonal activation. Interestingly, in healthy control subjects, 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 finding is consistent with other lines of evidence, including that from Samejima et al. (18) who demonstrated that the ratio of change in HR to change in log of norepinephrine (delta HR/delta log norepinephrine), an index of sinoatrial node sympathetic responsiveness, decreased progressively with the severity of HF. Consequently, it appears that at least 1 mechanism responsible for this derangement has been determined, which will facilitate approaches to address this potential therapeutic “target.”

An important finding of the investigation by Benes et al. (14) was the prognostic impact of resting HR and HR reserve, both independently and collectively, in these advanced HF patients. Over a mean follow-up of 469 days, 28 patients (34.6%) experienced an adverse event. Patients with a low resting HR (≤67 beats/min) had a lower risk of adverse outcomes than did those in the upper quartile of resting HR. The prognostic power of a reduced resting HR in HF has been seen in several large clinical trials, even with high rates of beta-blocker use (13). In contrast, patients in the lowest quartile of HR reserve (<0.38) displayed increased risk of adverse outcomes (14). Furthermore, the combined quartile analysis of resting HR and HR reserve provided incremental prognostic information with the highest risk (hazard ratio: 7.95, p = 0.002) if both parameters were abnormal. Thus, a high resting HR combined with a low HR reserve portended the worst prognosis for advanced HFrEF patients.

The study by Benes et al. (14) provides the best clinical and mechanistic insights to date for this important yet unappreciated “Cinderella” of HF pathophysiology. Now that they have helped reveal her true nature and beauty, this should help pave the way for overdue, novel therapeutic advances.

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REFERENCES


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