Chronotropic incompetence: a never-ending story

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This editorial refers to ‘Chronotropic incompetence and autonomic dysfunction in patients without structural heart disease’ by T. Kawasaki et al., on page 561.

A clear association between chronotropic incompetence and increased mortality has been established by a variety of studies in patients with coronary artery disease as well as in healthy individuals.¹,² These results gave rise to speculation that rate responsive stimulation might improve prognosis in pacemaker (PM) patients with concomitant chronotropic incompetence. To date, however, no study was able to show a reduction in mortality by rate responsive pacing. In contrast, some evidence even suggests that rate responsive stimulation is deleterious in heart failure patients.³,⁴ In PM patients with preserved left ventricular ejection fraction, a number of trials demonstrated the beneficial effects of rate responsive pacing on exercise capacity and cardiovascular response to exercise. However, data on these rather weak endpoints are conflicting as several studies published negative results. In our opinion, an important factor contributing to these inconsistent data lies in the lack of a standardized definition of chronotropic incompetence. Most commonly, chronotropic incompetence is defined as the inability to reach 85% of the maximum age-predicted heart rate (MPHR)⁵ which is generally calculated using Astrand’s formula, i.e. 220 minus age.⁶ Not least due to different definitions of chronotropic incompetence as well as an inconsistent methodology (e.g. trials with and without antiarrhythmic drugs), the reported prevalence of chronotropic incompetence ranges remarkably between 9 and 84% in PM patients.⁷

Another issue regarding rate responsive pacing is the question whether currently used sensors are sufficient. In addition to activity-based sensors (e.g. accelerometer and piezoelectric crystals), more physiological sensors (e.g. minute ventilation, peak endocardial acceleration sensor, and closed loop stimulation) are available. Owing to their robustness, activity-based sensors are used most frequently in the clinical routine, despite their known disadvantages. Physiological sensors are employed less often and are only available in rather costly devices. In the past, physiological sensors have often failed to meet the expectations of physicians and should therefore not be used uncritically. In accordance with our clinical experience, previous trials yielded conflicting results regarding the ‘optimal’ sensor.⁸,⁹ As no current type of sensor can be considered optimal, the RR mode has to be optimized individually for most patients, which is often time-consuming.

A crucial aspect of the debate on chronotropic incompetence is the fact that the underlying causes of chronotropic incompetence are still not completely understood. Early studies showed that heart rate during exercise is regulated by a reduction of vagal activity, an increase in sympathetic outflow, and by the relative sensitivity of the sinoatrial node to catecholamines.¹⁰ This interplay can be affected in patients with cardiovascular disease. In chronic heart failure, for example, the increased sympathetic activity and the diminished β-receptor density may influence heart rate regulation during exercise.³

Kawasaki et al.¹¹ provide new insights into mechanisms of chronotropic incompetence. To elucidate whether impaired autonomic function plays a role in the pathogenesis of chronotropic incompetence, the authors analysed heart rate variability in 172 subjects without evidence of cardiac disease undergoing exercise tests. For diagnosis of chronotropic incompetence, one of the following three criteria had to be met: failure to reach 85% of the MPHR, a heart rate reserve of <80%, or a chronotropic response index below 0.80 at submaximum workload. Out of 172 test subjects, 72 (41.9%) were found to have chronotropic incompetence. After exercise, the high-frequency (HF) component decreased in both groups to a similar extent. As the HF component is considered to be largely dependent on vagal activity, the authors conclude that vagal withdrawal occurred in both groups alike. In contrast, there was a significant difference between both groups in the decrease in the low-frequency (LF) component after exercise. Furthermore, the LF/HF component ratio only increased significantly in individuals with chronotropic incompetence and did not change in the absence of chronotropic incompetence after exercise. Although there is less consensus on the factors influencing the LF component, the authors deduce from their
data that sympathetic activation was induced in subjects with chronotropic incompetence after exercise. However, this sympathetic activation did not result in a physiological heart rate increase. Kawasaki et al. speculate that this phenomenon might be caused by a post-synaptic desensitization of the β-adrenergic pathway in the sinoatrial node due to a down-regulation of β-receptors in response to frequent sympathetic activation. Further studies are needed to find evidence for this interesting hypothesis.

Despite great scientific efforts, many questions regarding chronotropic incompetence remain unanswered to date. We believe, however, that—as recommended by European guidelines—the RR mode should be activated in PM patients with preserved left ventricular function and signs of chronotropic incompetence. Although this approach most likely has no influence on overall prognosis, it may improve exercise capacity and quality of life. In contrast, the rate adaptive mode should only be used with great caution in heart failure patients.

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References