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Noninvasive assessment of cardiac parasympathetic function: postexercise heart rate recovery or heart rate variability?

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POSTEXERCISE HEART RATE (HR) recovery (HRR) and HR variability (HRV) are commonly used in noninvasive assessment procedures for the determination of cardiovascular parasympathetic function (3, 8, 9, 15, 20). Evaluation of cardiovascular parasympathetic function is important because several clinical studies have documented a negative relationship between a background high in parasympathetic activity and the progression of cardiovascular disease (1, 8, 20). For example, a delay in HRR, a measure indicative of a reduced parasympathetic activity, has been observed in patients with chronic heart failure (8). In addition, a decrease in parasympathetic and/or an increase in sympathetic HRV indexes have been observed in patients with cardiovascular disease (20).

The recovery of HR following exercise typically progresses in a decreasing monoexponential fashion (18), and HRR can be quantified by 1) taking the absolute difference between the final HR at exercise completion and the HR recorded following 60 s of recovery (HRR_{60s}) (3, 8), 2) taking the time constant of the HR decay obtained by fitting the postexercise HRR into a first-order exponential decay curve ($HRR\tau$) (18), or 3) analyzing the first 30 s of HRR via semilogarithmic regression analysis (T30) (13) (Fig. 1). Since the initial rapid decline in HR is almost unaffected by variables such as exercise intensity and sympathetic blockade but is instead predominantly influenced by parasympathetic blockade, it has been suggested that short-term HRR indexes (i.e., T30 and HRR_{60s}) could be considered as markers of cardiac parasympathetic outflow (13, 15). In contrast, the second slow HR decay phase (included in $HRR\tau$), generally believed to be workload dependent (4, 13, 18), is thought to be related to the gradual withdrawal of sympathetic activity and to the clearance of stress system metabolites (i.e., plasma epinephrine, lactate, H^+ , P_i , etc.) following high-intensity exercise (18).

During stationary resting conditions, various maneuvers, such as controlled breathing, muscarinic blockade, or cold face immersion, have shown that the so-called high-frequency components of HRV (0.15–0.5 Hz), and, consequently, the extent of the root mean square of successive R-R interval differences (rMSSD) are predominantly generated by respiratory modulation of the cardiac parasympathetic outflow (19). Recently, time-varying analysis of HRV during recovery from exercise in humans (i.e., rMSSD calculated on consecutive 30-s windows; Fig. 1) has been used to capture the instantaneous level of parasympathetic reactivation (4). Moreover, it is now accepted

that the vagal-related HRV indexes more reflect the magnitude of modulation in parasympathetic outflow as opposed to an overall parasympathetic tone per se (12).

Because of the presumed parasympathetic origin of both HRR and vagal-related HRV indexes, it is intuitive to expect an association between these variables; however, studies have failed to find a relationship (3, 14). In fact, parasympathetic reactivation after intense exercise has been shown to be nearly abolished despite an almost preserved HRR (4). The lack of association between HRR and HRV might be due to factors that are known to interfere with parasympathetic outflow during the postexercise recovery phase or resting conditions, such as sympathetic activity or ventilation. It is also possible that these measures might characterize distinct independent aspects of cardiac parasympathetic function (6, 9).

As recently shown, the effect of parasympathetic drive on HRR is not as evident as previously believed (4, 17). Following varying degrees of aerobic and anaerobic energy contributions to an exercise task, we recently observed a strong relationship between T30 and total anaerobic participation (4). This finding suggests that the selective assessment of parasympathetic activity from short-term HRR after supramaximal exercise should be reconsidered. The diminished vagal tone (or its reduced effect on HR) following supramaximal exercise might be attributable to the upregulation of sympathetic activity incurred subsequently to such a demanding exercise task (4). Indeed, sympathetic withdrawal has recently been confirmed to be a major contributor to early HRR (15). Moreover, various investigations have demonstrated complex interactions between the sympathetic and vagal systems with respect to HR regulation, resulting in reduced or amplified vagal stimulation, dependent on the type and site of adrenergic receptors most selectively activated under given conditions (17).

The presumption of vagal activity based on HRV has not been without its limitations. Environmental conditions (noise, light, temperature, etc.) can exert a marked influence on HRV parameters and show a tendency to shift sympathovagal balance toward sympathetic predominance (19). Quiet sleep recordings (i.e., slow-wave sleep), characterized by a regular respiratory rate, have thus been proposed as an optimal recording condition to accurately assess parasympathetic function from HRV analysis (2). Moreover, HRV is not always linearly related to parasympathetic outflow (10). Various laboratory and ambulatory studies (6, 7, 10, 16) have described a saturation of cardiac parasympathetic regulation. A heightened vagal tone may give rise to sustained parasympathetic control of the sinus node, which may eliminate respiratory heart modulation and reduce HRV.

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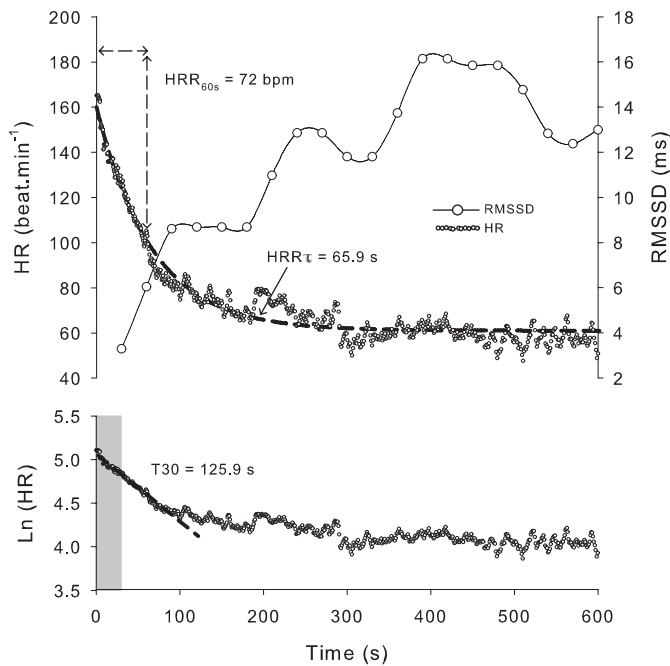


Fig. 1. Example determination of heart rate (HR) recovery (HRR) indexes and parasympathetic reactivation in a single subject following submaximal exercise (see main text for details). Gray shading represents initial 30-s period from which T30 is calculated. HRR_{60s}, HR recorded following 60 s of recovery; HRR τ , postexercise HRR into a first-order exponential decay curve; rMSSD, root mean square of successive R-R interval differences (30-s windows); bpm, beats/min.

Based on the culmination of these data, our current understanding is that the parasympathetic system is not the unique determinant of HRR and vagal-related HRV indexes and that, instead, there could exist an observed dissociation phenomenon between efferent vagal outflow and its effect on HR. In a recent descriptive investigation, we suggested that the two measures might bring separate but complementary information pertaining to cardiac parasympathetic function (3). We found that HRR was strongly related to weekly training load but that the vagal-related HRV indexes were more associated with cardiorespiratory fitness (as assessed by maximal oxygen uptake). These combined findings suggest that parasympathetic function may be influenced by both endurance conditioning and genetics. Although our findings could suggest that parasympathetic outflow might differentially affect HR level (HRR) and HR modulation (HRV), we lacked clinical data to make any firm conclusions on the matter.

In this issue of the *American Journal of Physiology-Heart and Circulatory Physiology*, Dewland et al. (9) present novel and rational data showing differences between physiological determinants of HRR and HRV. In this study, the authors elegantly used acetylcholinesterase inhibition with 30 mg pyridostigmine to significantly decrease resting HR and increase postexercise HRR compared with placebo in sedentary subjects but not in trained athletes; the drug also had no effect on resting vagal-related HRV indexes. Since pyridostigmine maintains acetylcholine concentration in the neuroeffector gap (see references in Ref. 9), the drug mimics an overall increased parasympathetic outflow condition. Because HR is closely dependent on acetylcholine concentration at the muscarinic receptors in the heart, the pyridostigmine effect is consistent

with that of a decreased resting HR and that of an augmented HRR observed in sedentary subjects (see references in Ref. 9). In contrast, pyridostigmine administration has no known effect on the magnitude of parasympathetic outflow modulation (see references in Ref. 9). This latter observation is consistent with the lack of change in HRV indexes. Taken together, these findings confirm, at least in the sedentary state, that HRV vagal-related indexes might reflect parasympathetic modulation (12). The results also suggest that HRR, preferably measured after submaximal exercise (i.e., below the first ventilatory threshold) to avoid possible sympathetic activity interference (13, 18), might be preferentially used to approximate vagal tone.

As proposed by Dewland et al. (9), the lack of either a reduction in resting HR or an improvement HRR in trained athletes after pyridostigmine administration might be related to the attainment of a “ceiling effect” in training status or to a “saturation” of vagal modulation. Nevertheless, a saturation phenomenon has been reported to affect HRV parameters but not HR per se (6, 7, 10, 16). Although morphological modifications can play a role (i.e., left ventricular hypertrophy), a strong vagal tone is thought to be the major determinant of the low resting HR observed in “saturated” athletes. In other words, we believe that the modulation rather than the tone might be saturated. Improved knowledge of the physical activity profile [i.e., moderate vs. vigorous habitual physical activity (5)] and the fitness level of the athletes of Dewland et al. (9) would have assisted to compare their results with those from previous studies. Plotting HF power density against R-R interval length, as proposed by Kiviniemi et al. (16), might have also assisted to confirm this supposed saturated state. Furthermore, the lack of a pyridostigmine effect on HR in trained subjects is interesting. It could be hypothesized that the regulated and effective parasympathetic effect on HR stimulated by other parasympathomimetic factors [i.e., baroreflex-increased parasympathetic activity produced by phenylephrine infusion (10) or by chronic aerobic conditioning (6, 7, 16)] is not only mediated via sinoatrial signaling (11). Indeed, HR has recently been reported to be peripherally controlled by two interacting cardiac centers: the sinoatrial node (selectively affected by pyridostigmine) and the posterior atrial ganglion (11). To extend our understanding of the distinct determinants of HRR and HRV, future research is needed to compare the effects of regulated (via baroreflex loop) versus exclusively peripherally (drug) stimulated parasympathetic outflow on HRR and HRV.

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