Exercise, Heart Rate Variability and Longevity:
The Cocoon Mystery?

Running title: Poirier; Heart rate variability and exercise

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Humans are increasingly approaching an era where cardiovascular health seems to be one of the major upper limits on achievable lifespan. An increasing body of scientific research and observational evidence indicates that resting heart rate (HR) is inversely related to the lifespan among homeothermic mammals and within individual species. Heart rate not only reflects the status of the cardiovascular system, but also serves as an indicator of cardiac autonomic nervous (sympathetic and parasympathetic) system activity and metabolic rate. There is a remarkable amount of variation in HR among species, it can be as low as 30–35 beats per minute (bpm) in large animals like whales and elephants, or as high as 600–700 bpm in mice (Figure 1). Mammals that have slower average HR tend to live much longer than those that have faster HR. Although some variability inevitably exists and is observed in human, estimations yield a mean value of around 1 x 10^9 (1 billion) heartbeats in a lifetime across almost all homeothermic mammals (Figure 2).

Regularly engaging in moderate-to-vigorous physical activity has been shown to reduce the risk of all-cause mortality, cardiovascular mortality, cancer mortality, stroke, heart disease, breast cancer, colon cancer, as well as numerous other undesirable health outcomes. Endurance physical exercise can reduce HR and promote overall health profile. It is well known that endurance athletes tend to have higher parasympathetic tone and lower resting HR than the general public. While exercise itself elevates HR significantly, resting HR is significantly reduced and overall total heartbeats over 24 hrs are reduced as well. There is also a powerful association between functional capacity and cardiovascular risk.

Autonomic nervous system function is assessed clinically by measuring resting heart rate, heart rate variability (HRV), or heart rate recovery following exercise. Heart rate variability is modulated by many physiologic or pathologic states. Adjustments from the sympathetic...
modulations are slow, on the time scale of seconds, whereas those from the parasympathetic are fast, on the time scale of milliseconds. Thus, the parasympathetic influences will generate more rapid changes in the beat to beat regulation of the heart. There is extensive literature documenting a number of determinants of autonomic tone\textsuperscript{6,7}. Human heart rate is not regular and varies in time and such variability, also known as HRV is not representing ‘background noise’, or a random phenomenon\textsuperscript{8}. These variations are thought to be the result of complex interactions between extrinsic environmental and behavioural factors and intrinsic cardiovascular regulatory mechanisms (neural central, neural reflex, and humoral influences) that are not yet completely understood\textsuperscript{9}. Nevertheless, HRV is a surrogate index of cardiac autonomic nerve function and a marker of imbalanced sympathetic/vagal activities (sympathetic tone enhancement and/or vagal tone depression). Heart rate variability also independently predicts cardiovascular disease mortality not only in patients with coronary artery disease or chronic heart failure but also in apparently healthy populations\textsuperscript{10-12}. Many different HRV measures exist. Most clinicians are unfamiliar with HRV indices, and the non electrophysiologists are invited to look at Table 1 of the manuscript of Soares-Miranda et al.\textsuperscript{13} for a better description of HRV indices. Succinctly, using linear algorithms, HRV is usually clinically analyzed in the time or frequency domain. Time domain indices are the first to be used and the simplest way to calculate HRV. They are mathematical calculations of consecutive RR intervals, and they correlate with each other (SDNN, SDANN, pNN50, etc.). Frequency domain indices are more elaborated and based on spectral analysis, mostly used to evaluate the autonomic nervous system contribution to HRV (VLF, LF, HF, HF/LF ratio). Spectral analysis of heart rate signals provides their power spectrum density and displays in a plot, the relative contribution (amplitude) of each frequency, after application of a Fast Fourier transformation to the raw signal. The area under the power
spectral curve in a particular frequency band (power) is considered to be a measure of HRV at that frequency \(^{14-16}\). Spectral analysis can be used to analyze the sequence of RR intervals of short-term recordings (2 to 5 minutes) or an entire 24-hour period (Holter monitoring)\(^{14}\). Hence, HRV indices represent the final outcome of complex systems. ULF power correlates with SDNN and SDANN index; VLF power and LF power with SDNN index; and HF power with RMSSD and pNN50 \(^{17}\).

Soares-Miranda L et al.\(^{13}\) evaluated cross-sectionally and longitudinally measures of both physical activity (PA) and 24-hour Holter HRV over 5 years among 985 older US adults in the community-based Cardiovascular Health Study. They reported that greater total leisure-time activity, as well as walking alone, were prospectively associated with healthier cardiac autonomic function (assessed with HRV). Greater total leisure-time activity, walking distance, and walking pace were each prospectively associated with specific, more favorable HRV indices and over 5 years, those who increased their walking pace or walking distance had more favorable HRV indices when compared with those that decreased their walking pace or walking distance.

The authors evaluated PA in pre-specified categories, including: for leisure-time activity (quintiles), exercise intensity (none/low, medium/high), blocks walked (quintiles), and usual pace walked (<2, \(\geq 2\) mph). Usual leisure-time activity was assessed at baseline (1989-90) and at 1992-93 using a modified Minnesota Leisure-Time Activities questionnaire. As pointed out by the authors, the modified Minnesota PA questionnaire has been validated against the full version. Although it is recognized that self-reported measures of PA may be susceptible to bias, measures of PA may be sufficient for ranking individuals within an epidemiological dataset for analysis \(^{18}\). Strength of the study is the utilization of 24-hour measurements that assess both short-term and long-term HRV indices where short-term ECGs, which have been reported in numerous other
epidemiological studies, assess only short-term HRV indices. Surprisingly, PA variables were not significantly associated with other HRV indices, including rMSSD, NLF, NHF, LF/HF ratio, or VLF power whereas faster walking pace was associated with higher nighttime LF/HF ratio only. It is important to emphasize that rMSSD, NLF, NHF and LF/HF ratio were evaluated among individuals (n=493) with lower erratic HRV. Lower statistical power due to the smaller numbers of subjects may explain the lack of statistical association since regular PA is generally associated with more favorable HRV indices, especially those reflecting increased vagal modulation and reduced sympathetic activity. On the other hand, the participants in the highest quintile of changes in walking distance had significantly higher ULF power, compared with the lowest quintile. Similarly, those that increased walking pace had significantly higher HRV indices when compared to those that decreased or maintained their walking pace. While the biologic interpretation of some indices is complex, the meaning of ULF is uncertain. Mean daytime heart rate was 78±10 bpm, ranging from 71 to 85 bpm. One may assume that these older participants were not very physically active during daytime especially with the use of only 13% β-blocker in the population studied. One must remember that intrinsic (denervated heart) HR is higher than the normal resting HR since the heart is under tonic inhibitory control by parasympathetic influences. Indeed, the intrinsic heart rate of healthy individuals, as reflected by the heart rate observed during complete autonomic blockade, is ~100 bpm. With advancing age, the intrinsic rate decreases, particularly in the latter decades of life. More detailed studies have investigated the pattern of loss of autonomic function during aging and have demonstrated that HRV parasympathetic activity decreases faster until the age of 80 and then it starts to increase again. Even if a range of covariates were available and evaluated as potential confounders (body mass index, systolic blood pressure, use of beta-blockers, calcium channel-blockers, or
digitalis, and presence or absence of coronary heart disease, congestive heart failure, hypertension, diabetes, or left ventricular hypertrophy) and findings were similar in several sensitivity analyses, residual confounders due to unknown or incompletely measured factors cannot be excluded. Body mass index is certainly not a good reflection of adiposity and fat distribution in older population. Indeed, body fat distribution, independently of BMI, may modulate HRV. This may be of clinical importance since sarcopenic obesity and physical disability are encountered in the aging older population and is characterized by decreased muscle mass and increased fat mass, particularly visceral fat. Also, the rate of diabetes patient was low (15%). This is important since abnormal HRV has been associated with the severity of left ventricular diastolic dysfunction which has been associated with lower exercise capacity in well-controlled type 2 diabetes subjects.

The study of Soares-Miranda et al. is an interesting prospective valuable study, and showed the independent link between PA and preserved autonomic function in older patients. Although several studies have reported on the clinical and prognostic value of HRV analysis in the assessment of patients with cardiovascular diseases, this technique has not been incorporated into clinical practice. To welcome HRV analysis as part of cardiovascular risk assessment, prospective, randomized studies focusing on the clinical utility of HRV as a cardiovascular risk marker in primary or secondary prevention or as a tool to assess treatment efficacy are required. Meanwhile, the findings of Soares-Miranda et al. may be used for knowledge transfer to older people to reinforce the positive impact of habitual physical activity later in life.

Conflict of Interest Disclosures: None.
References:


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**Figure Legends:**

**Figure 1.** Semi logarithmic relation between resting heart rate and life expectancy in 15 mammals species. Excluding humans, HR is inversely correlated with lifespan. Adapted from 1.

**Figure 2.** Relation between life expectancy and total heartbeats over a lifetime of 15 mammal species. Data fall in a relatively narrow range ~ 1 billion beats. Adapted from 1.
Figure 1

Heart Rate (beats/min)

Life Expectancy (years)

Mouse
Hampster

Rat

Monkey
Marmot

Cat

Dog

Tiger

Ass

Giraffe

Horse

Elephant

Whale

Whale

Man
Figure 2
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