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Invited editorial

Heritability analyses of resting heart rate: Is it relevant?

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In this issue of the journal, Xhaard and colleagues[1] investigate the heritability of resting heart rate (RHR) using the data from the STANISLAS family cohort. This study evaluated RHR heritability in individuals with a mean age of 33.6 (±16.7) years, participating in four different visits, over 20 years of follow-up. Their results indicated a correlation between parental and offspring RHR ($r^2 = 0.13$; $P < 0.01$), of which approximately 25% was estimated to originate from the genetic background and 25% from individuals' environmental factors (i.e. estimated from repeated RHR measures). They showed that heritability estimations were sensitive to the time point that might, at least partly, account for the large heterogeneity (14–39%) of RHR heritability estimations.

RHR has been recognised as a modifiable prognostic marker of health and disease across many different ancient cultures.[2] According to the Greek physician, Galen (AD 130–200), among the 27 features of the pulse that can be recognised, RHR was the most important feature related to individuals' health. RHR is commonly considered as an indicator of the balance between the sympathetic and parasympathetic nervous system with the antagonistic role from the parasympathetic nervous system in co-regulating heart function.[3] The RHR in humans ranges between 60 and 100 beats per minute (bpm), with substantial variations over the day altered with different situations.4[4] It is also linked to individuals' characteristics in which women are more likely to have higher RHR compared to men.[5]

There are several theories on why RHR might be an important marker, possibly causally, linked to healthy ageing and the development of disease. In 1997, Levine presented a hypothesis based on the inverse relationship between RHR and longevity in mammals, with the exception of humans, in which large animals such as elephants with a slow RHR of 15–30 bpm live 20–30 years, while small animals such as mice with a high RHR of 400–600 bpm live 1–3 years, suggesting a mean value of 10×10^8 heart beats per lifetime (Figure 1).[2] This may link to the fact that when the heart beats faster it has to use more oxygen; it has been theorised that RHR is an important marker of the basal metabolism which ultimately determines longevity.[6] The ecological observation by Levine supports studies so far about the impact of RHR on health and disease development in humans. Recently, Eppinga et al. presented human data supporting this theory. Using a Mendelian randomisation approach, including 265,000 individuals from the general population, the authors also provided evidence for a causal link between RHR and longevity.[7]

In many studies, both in healthy individuals as well as in patients with (cardiovascular) diseases, an increased RHR is a strong independent predictor of mortality and morbidity.[8] Although the magnitude of these associations varies across studies, a recent meta-analysis suggests that every 10 bpm increased RHR has been associated with a 9% and 8% increased risk of all-cause mortality and CVD mortality, respectively.[9] However, this does not prove causality of RHR itself, it might be due to confounding factors such as adrenergic activation affecting both RHR as well as mortality. However, the most intriguing question may arise as to whether lowering RHR, for instance from 70 to 60 bpm, has a direct effect on the length of life. Several animal studies have investigated the effectiveness of heart rate-lowering drugs; for example, beta-blockers or selective sinus node inhibitors. These studies observed that a reduction of RHR by 50% was associated with an increased life span of ±20%.[6] Trials of beta-blockers and calcium antagonists also demonstrated survival benefit closely related to the reduction in RHR in patients post-myocardial infarction and heart failure.[6] Whether a reduction in RHR

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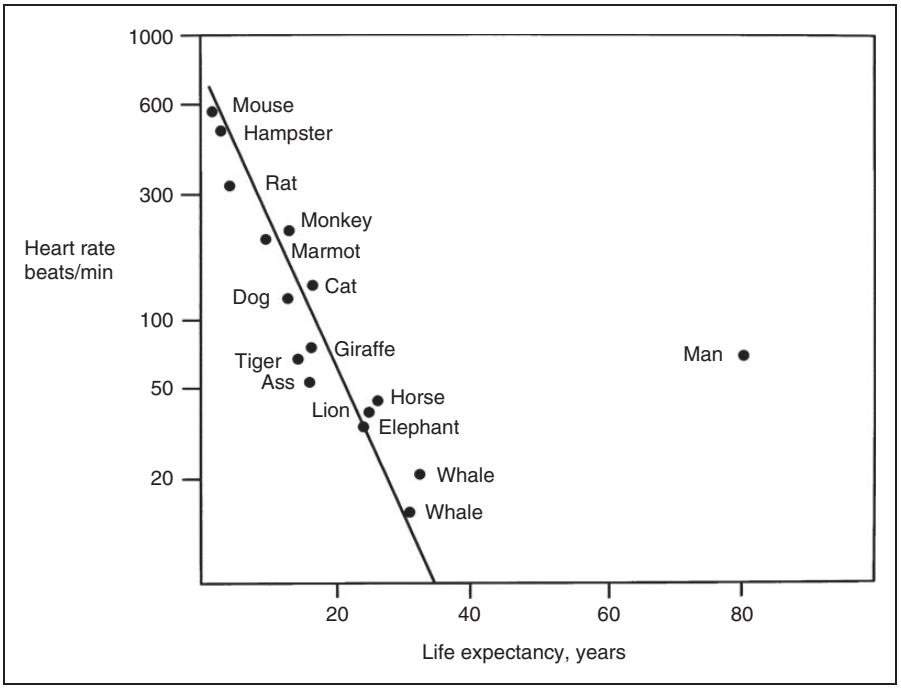

Figure 1. Semilogarithmic relationship between resting heart rate and life expectancy in mammals (amended from Levine, 1997).[2]

per se can be translated into long-term clinical benefits deserves future studies.

Many different factors have been identified that have an effect on RHR; for example, lifestyle factors, hormonal alterations and genetic factors.[6] If RHR is indeed causally linked to health and disease, extensive knowledge on modifiers, including its heritability components might be of paramount importance to improve healthy ageing. A genome-wide association study (GWAS) on 134,251 individuals has recently reported the association of 64 genetic variants with RHR, 46 of these were novel; the amount of variance in RHR explained by these 64 loci was 2.5% ($P < 5 \times 10^{-8}$).[7] This suggests that RHR represents a combined effect from several non-genetic factors. The literature so far on heritability estimates of RHR among healthy individuals is highly heterogeneous, with the results ranging from 14% to 65% in different studies. While the heterogeneity may be due to the characteristics of the population studied, it could be explained by different methods, study designs and the residual confounding effects of non-genetic factors.

Compared to previous findings from family and twin studies, the results of the study by Xhaard and colleagues showed a lower contribution of genetic factors (25%) to RHR.[1] The lowest heritability estimated by that study belonged to the subset of children ($n = 4252$, 53%) with a mean (SD) age of 14.3 (3.9) years. Despite the fact that the results may highlight the contribution of non-genetic rather than genetic factors influencing RHR in the paediatric population, the results might also be due to the fact that assessing RHR in children is more challenging.

The study performed by Xhaard and colleagues[1] is a methodologically well designed study in a large population ($n = 10{,}142$), of which 4928 (49%) had GWAS data. The authors tested RHR heritability from multiple time point measurements (every 5 years), in four visits over a 20-year follow-up. Among 4928 individuals genotyped, 1553 (32%) had more than one RHR measurement during the follow-up and the majority ($n = 685$) had three measurements. The study used a linear mixed model at multiple time points. The statistical method simultaneously included both genetic variants and common environmental effects shared by families fitted within the fixed effects part. The study was based on self-reported pedigree or the genetic relatedness matrix (GRM). The GRM estimates the genetic relationship between individuals with repeated measures of RHR. Although the use of GRM calculated based on GWAS data provides a more accurate estimation of heritability, the results of both methods including self-reported pedigree (in all individuals) and GRM (only in the subset of genotyped individuals) were very similar. This gives weight to the results of previous studies on the reliability of self-reported measurements, a simple inexpensive way to measure RHR.[10] Several factors should be taken into account when interpreting the findings. Notably, a question may arise as to whether a single RHR measurement reflects

the heart rate pattern during the whole day and from day to day. Xhaard and colleagues report on the variability of RHR, but throughout the paper the terminology of heart rate variability (HRV) is used, which might be confusing to some readers interested in changes in time intervals between heart beats and the inter-beat intervals. HRV analyses and metrics have been developed to characterise further the autonomic background of heart rate, and are usually determined on 24-hour registrations of the electrocardiogram.[11] The study did not investigate HRV but rather the variability of RHR. The study is also limited by investigating the heritability of HRV for each individual during follow-up. The HRV measurement, which is a proxy of healthy cardiac functioning, could help to study the progression in clinical outcomes as well as to test the optimal efficacy of interventions. As the study included participants from different visits, an important part of the variation in RHR, approximately 25%, was attributed to the repeated measures, which might be due to changes in methods of RHR measurement over a 20-year follow-up. This may imply that a standardised procedure of RHR measurement undertaken in clinical studies would be of importance. Moreover, the analyses were adjusted for several known risk factors including age, sex, tea or coffee consumption, beta-blocker use, physical activity, tobacco and alcohol consumption. However, the possibility still remains that some unmeasured factors, for instance insulin resistance, body mass index, stress and hyperlipidemia may have an impact on RHR indices and could therefore lead to some residual confounding. In addition, only a small non-random subset of the cohort had genetic data available. This subset included the participants who were older and might have had different characteristics, and could, therefore, affect the study conclusions. Finally, the study was performed in a highly selected population. Thus, the results await further confirmation in other cohorts and might not be easily generalisable to most populations.

Clinical and research implications

There is a continuous interest in RHR and its heritability but is it of interest?

Given that RHR is believed to be causally linked to health and disease, RHR measurement as a simple part of every clinical examination should be considered. Driven by new technologies, measuring RHR as one of the early markers in a wide variety of both cardiac and non-cardiac disorders becomes applicable for many individuals, either alone or combined with the other risk factors. New digital devices; for example, specific heart rate apps for mobile phones and watch bracelets make a reasonably accurate self-measured RHR possible for the public as well as for clinicians providing future perspectives of incorporating knowledge of RHR in personalised preventive strategies.

Assuming there is a genetic causal link, addressing the full complexity of individuals' RHR variability, taking to account gene–environment interaction also warrants future research. However, given that RHR heritability is low, it appears that the effect from non-genetic markers including lifestyle/environmental factors, physiological and neuropsychological factors is substantially high. We believe that there is a need to focus on potential modifiable components of RHR in diverse populations, possibly to help tailor interventions targeting this important cardiovascular disease risk marker.

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