De battre mon coeur s’est arrêté—Movie by Jacques Audiard.

Resting heart rate (RHR) is one of the simplest cardiovascular parameters, which usually averages 60 to 80 beats per minute (b.p.m.), but can occasionally exceed 100 b.p.m. in unconditioned, sedentary individuals and be as low as 30 b.p.m. in highly trained endurance athletes. Epidemiological evidence demonstrates that RHR, or its corollaries, namely post-exercise heart rate recovery, which is mediated primarily by vagal tone, and heart rate variability (HRV, beat-to-beat variability also mediated by autonomic nervous system, especially parasympathetic) correlates with cardiovascular morbidity and suggests that RHR determines life expectancy. Multiple studies have identified RHR as an independent risk factor for cardiovascular disease (comparable with smoking, dyslipidemia or hypertension). However, it is often overlooked.

Heart rate: an independent cardiovascular risk factor

Since 1980, it is known that resting heart rate (RHR) is a prognostic factor in coronary diseased patients. Data from the Coronary Artery Surgery Study (CASS) published last year underline the prognostic importance of RHR for morbidity (time to rehospitalization), as well as total and cardiovascular mortality. Heart rate proves to be the best predictor after myocardial infarction, in patients with congestive heart failure, as well as in patients with diabetes mellitus or hypertension.

In addition, it was found that elevated RHR is also strongly associated with mortality in the general population. For instance, in the Framingham Study, in a cohort composed of 5070 subjects who were free from cardiovascular disease at the time of entry into the study, cardiovascular and coronary mortality increased progressively with RHR (Figure 1). In a subset of 4530 untreated hypertensive (\(>140\text{ mmHg systolic or } >90\text{ mmHg diastolic} \)) patients included in this study, using 36-year follow-up data, odds ratio (OR) for each increment in heart rate of 40 b.p.m. were 1.68–1.70 (CI: 1.08–2.67) for cardiovascular mortality and 1.59–2.88 (CI: 1.59–2.88) for all-cause mortality. This latter study, or heart rate of 40 b.p.m. were 1.68–1.70 (CI: 1.08–2.67) for 36-year follow-up data, odds ratio (OR) for each increment in subset of 4530 untreated hypertensive (cardiovascular mortality and fascinatingly also 2.14–2.18 mortality increased progressively with RHR 6 (the time of entry into the study, cardiovascular and coronary death was 1.35 (CI: 1.01–1.80) in the group with RHR 60–80 b.p.m. to 2.18 (CI: 1.37–3.47) in the group with RHR >100 b.p.m. Data from the National Health and Nutrition Examination Survey (NHANES I) Epidemiologic follow-up study confirmed this association in white men (RR: 2.23, CI: 1.4–3.6, RHR >90 vs. <70 b.p.m.) and cardiovascular mortality after controlling (in various statistical models) for manifold recognized risk factors. Filippovych et al. (PPS) found that mortality could be predicted by resting heart frequency in 4907 middle-aged males followed during 17 years. Seccareccia et al. (MATISS) verified that in a low-risk Italian population, heart rate increment was associated with a relative risk increase from 1.52 (CI: 1.29–1.78) for all-cause mortality, 1.63 (CI: 1.26–2.10) for cardiovascular mortality, and 1.47 (CI: 1.19–1.80) for non-cardiovascular mortality.

As with cholesterol levels, the risk is graded, i.e. the risk rises with increasing RHR. In the French IPC trial, Benetos et al. evaluated the prognostic value of RHR on mortality in more than 19 000 healthy subjects and found a continuous, graded effect of RHR during a mean follow-up duration of 18.2 years. In men, the relative risk for cardiovascular death was 1.35 (CI: 1.01–1.80) in the group with RHR 60–80 b.p.m. to 2.18 (CI: 1.37–3.47) in the group with RHR >100 b.p.m. Data from the National Health and Nutrition Examination Survey (NHANES I) Epidemiologic follow-up study confirmed this association in white men (RR: 1.37, CI: 1.02–1.84, RHR >84 vs. <74 b.p.m.) and extended this observation to black men and women. This is an important finding because it has been considered that high RHR was only a weak predictor in the female gender. The key studies on the topic are listed on the Table 1.

<table>
<thead>
<tr>
<th>RHR (b.p.m.)</th>
<th>Mortality Risk Factor</th>
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<tbody>
<tr>
<td>&lt;70</td>
<td>1.29–1.78</td>
</tr>
<tr>
<td>70–80</td>
<td>1.26–2.10</td>
</tr>
<tr>
<td>&gt;84</td>
<td>1.19–1.80</td>
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On the basis of this evidence, it has been proposed that, as in animals, life span could be predetermined using allometric scales based on RHR. Longevity determination is a key element in biogerontology. Within the animal kingdom, the mammals’ heart rate represents an inverse semi-logarithmic relation to life expectancy: small
animals have a higher heart rate and shorter lifespan than do larger \( \times 10^8 \) (Figure 2). The average number of heart beats per lifetime in mammalian is unexpectedly constant within one order of magnitude, \( 7.3 \pm 5.6 / \sqrt{10^8} \) despite a 40-fold difference in longevity (Figure 3). As a corollary, the basal energy consumption per heart beat and heart mass may be the same for all animals. This suggests that the life span is predetermined by the basic energetics of the living cells, and that the apparent inverse relation between life span and heart rate reveals the heart rate to serve as a marker of the metabolic rate. This may be exemplified by considering the vast range of physiological cardiac parameters between one of the smallest, the shrew weighing 2 g, and the largest extant mammalian, the blue whale of 100 000 kg (Table 2 with data compiled from Dobson31). Despite a difference of many millions in body weight, heart weight, stroke volume, and total blood pumped per lifetime, the total oxygen consumption and ATP usage per unit mass and lifetime are almost identical together with the total number of the heart beats per lifetime.

Only humans make an exception to the rule by living longer and thus accumulating a larger mean number of heart beats of around \( \times 10^8 \) per lifetime (Figure 3). One might speculate how modern humans have stretched the biological boundaries by pushing the life expectancy to 80 years and beyond. The most likely explanations may be changes in life-style, drugs (in particular, antibiotics), prevention, and nutrition.28 However, the question should still be raised: does the RHR causally determine the life span, or is it only an epiphenomenon?

**High RHR: genetics vs. environmental factors?**

The last decade has witnessed key discoveries on mechanisms leading to isolated high RHR. Singh et al.32 highlighted
the contribution of genetic factors as a substantial determinant of RHR. Heritability analyses have been done by studying correlations between siblings and between spouse pairs after adjusting for important covariates within the Framingham Heart Study. They estimated the heritability of RHR to be 21%, which was similar to the subsequent report by Martin et al.'s estimate of 26%. Using a candidate gene approach for looking at the genetic determination of RHR, Ranade et al.34 found a ser49-to-gly (S49G) polymorphism in the beta-1 adrenergic receptor (ADRB1) associated with RHR. Serine homozygote subjects had the highest mean RHR. A finding, which was supported by results from a genome scan study by Wilk for quantitative trait loci influencing RHR in about 1000 Caucasians and 1000 African Americans. Wilk et al.35 (Hypertension Genetic Epidemiology Network-HyperGEN) also demonstrated that the highest logarithm of the odds (LOD) score was detected on chromosome 4. Further investigations by Martin et al.33 from the Metabolic Risk Complications of Obesity Genes project, obtained significant evidence of linkage (LOD = 3.9) for RHR on chromosome 4q, in the same region as for long QT syndrome 4 and within the 1-LOD unit support interval of two candidates: ankyrin-B and myozenin.

So is it only genetics? The response is clearly NO. Singh et al.32 demonstrated (apart from the genetic factors) that environmental causes (body mass index, systolic and diastolic blood pressure, smoking, and alcohol consumption) play at least such a large role in the determination of the RHR/HRV (13–40% vs. 13–23%). Martin et al.33 observed that individuals (especially females) with elevated RHR exhibited significantly elevated insulin and glucose levels, waist circumference, BMI, and diastolic blood pressure and suggestively elevated triglyceride levels and systolic blood pressure, all different clusters from the well known insulin resistance syndrome.36,37 The question is, therefore, whether high RHR also represents a member of this family. In line with these findings, recent studies have contributed importantly to generate the new concept that a defect in ‘bioavailability’ of nitric oxide (NO) plays a central role in the pathogenesis of this disorder. Interestingly, NO has been implicated in autonomic regulation of various aspects of cardiovascular system and could, thus, be the missing link between metabolic syndrome and high RHR (for review, see Sartori et al.38). In the coronary arteries, NO participates in parasympathetic vasodilation and inhibition of its sympathetic vasoconstriction.40 NO also modulates myocardial contractility in response to both cholinergic and beta-adrenergic stimulation.41,42 More importantly, NO is considered to modulate the autonomic control of heart rate, and, thus, RHR. Studies in humans suggest that NO augments cardiac vagal control in healthy subjects, as well as in patients with heart failure.44 Studies in animals established that this effect was mediated by the neuronal isoform of NO synthase (nNOS): mice (intact animals or isolated atria harvested from such animals) with complete deletion of

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Shrew</th>
<th>Blue whale</th>
<th>Fold difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight</td>
<td>2 g</td>
<td>100 000 kg</td>
<td>50 000 000</td>
</tr>
<tr>
<td>Heart weight</td>
<td>12 mg</td>
<td>600 kg</td>
<td>50 000 000</td>
</tr>
<tr>
<td>Heart weight over body weight</td>
<td>0.006</td>
<td>0.006</td>
<td>1.0</td>
</tr>
<tr>
<td>Heart rate per minute</td>
<td>1000</td>
<td>6</td>
<td>170</td>
</tr>
<tr>
<td>Life span (years)</td>
<td>1</td>
<td>118</td>
<td>118</td>
</tr>
<tr>
<td>Heart beats per lifetime</td>
<td>6.6 × 10^8</td>
<td>11 × 10^8</td>
<td>1.7</td>
</tr>
<tr>
<td>Stroke volume (litres)</td>
<td>1.2 × 10^-6</td>
<td>350</td>
<td>300 000 000</td>
</tr>
<tr>
<td>Cardiac output (litres per min)</td>
<td>0.001</td>
<td>2098</td>
<td>2 200 000</td>
</tr>
<tr>
<td>Total blood pumped per lifetime (litres)</td>
<td>800</td>
<td>1.3 × 10^11</td>
<td>163 000 000</td>
</tr>
<tr>
<td>Blood pumped (litres per lifetime per kg heart)</td>
<td>6.7 × 10^7</td>
<td>22 × 10^7</td>
<td>3.3</td>
</tr>
<tr>
<td>Total oxygen consumption (litres per kg per lifetime)</td>
<td>35 000</td>
<td>39 300</td>
<td>1.1</td>
</tr>
<tr>
<td>Moles ATP per kg per lifetime</td>
<td>7813</td>
<td>8771</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Data of column one and two were collected from Dobson.31
the gene display impairment in the parasympathetic control of heart rate. So, is high RHR an epiphenomenon of the same spectrum of disease, yet known as metabolic syndrome? The answer is probably affirmative.

Because virtually all widespread ‘common’ diseases, such as diabetes or hypertension, result from the complex interaction of genetic susceptibility factors and modifiable environmental factors, one should postulate that this is also the case for the pathogenesis of elevated RHR. In line with this concept, animals fed with high-fat diet (unfortunately a not-so-infrequent diet in humans) rapidly develop a loss of nocturnal dipping of both blood pressure and heart rate, and then all the pattern of metabolic syndrome. This effect is exaggerated in animal with NO deficiency, but could also happen with other gene deficiency, as demonstrated by PPAR, conditional E-null mice.

HR-lowering therapy on the myth of eternal youth

If heart rate conditioned the fate of basal energy consumption and that the total energy per life is predetermined, life span should depend on heart rate (as in everyday chassis battery): average (battery) life has become shorter as energy requirements have increased. Taking advantage of this theory, techniques aiming to lower RHR should increase the life span. In wildness, hibernation acts in this way: hibernation markedly lowers RHR and prolongs life. For example, hibernating bats’ heart rate decrease by 45-fold from 10–20 b.p.m. Hibernating bats live 70% longer (39 vs. 23 years) than its non-hibernating counterparts. In humans, modification of coronary heart disease risk factors play a key role in the control and alteration of the atherosclerotic process. Because hibernation is hardly possible (although by different mechanisms), reduce conductance velocity and cardiac inotropism, reduce coronary perfusion. BB have consistently been shown to reduce both the morbidity (risk of hospitalization) and the mortality. Multivariate analysis of CIBIS II showed that under beta-blockade, larger the discard of RHR was associated with, higher the survival and freedom of hospital admissions.

Should we prescribe HR-lowering drugs to patients with high RHR, but without known CAD or CHF?

In the general population, a pulse rate higher than 90 b.p.m. may be harmful. So, should we treat it with the same strength as other components of the metabolic syndrome (hypercholesterolemia, arterial hypertension, or obesity)? To date, no human study has been performed to demonstrate the efficacy, the risk-benefit ratio, or even less, the cost-effectiveness of heart-rate lowering treatment in patients without cardiac disorders. Few evidences exist, however, based on animal studies. In monkeys, heart rate reduction by sinoatrial node ablation or administration of propranolol is associated with a noticeable reduction of atherogenesis. In mice, administration of digoxin slowed the heart rate and prolonged the life span.

In humans, how should we currently manage high RHR? Since it could unmask hypoxaemia, anaemia, alcoholism, chronic stress or depression, or be the consequence of already prescribed drugs, a careful investigation should be done to exclude and, if necessary, treat secondary causes. Furthermore, lifestyle changes should be recommended with special emphasize on preventing anxiety, stress and toxics (caffeine, alcohol, nicotine, amphetamines, or cocaine), screen for drugs (hydralazine, thyroid hormones, catecholamines, aminophylline, etc.), and prescribe exercise or rational behaviour therapies. For instance, one should consider that pet ownership can lower RHR.

Besides the BB, some of the calcium channel blockers (CCB), such as diltiazem and verapamil (non-dihydropyridines), also potently reduce the heart rate. BB reduce both RHR and the response of the heart rate to exercise. The reduction of heart rate by BB is accompanied by a decrease in peripheral blood pressure with consequently reduced cardiac oxygen consumption and a longer diastolic filling time allowing for increased coronary perfusion. BB have consistently been shown to reduce cardiovascular mortality, sudden cardiac death, and reinfarction in patients recovering from previous infarction. In common with BB, the CCB of the non-dihydropyridine type also lower the heart rate and blood pressure as well as the risk of reinfarction. In principle, both classes of drugs operate by lowering the intracellular calcium signalling (although by different mechanisms), reduce conductance velocity and cardiac inotropism. Since it is known that the heart rate is primarily determined by the hyperpolarization-activated cation current, termed If (f stands for funny because of its unusual activation by hyperpolarization at voltages in the diastolic range), Ih or Iq, the search for drugs that reduce the heart rate without the aforementioned unwanted effects of BB or CCB is going on. In the heart, the pacemaker current is carried by a family of hyperpolarization-activated, cyclic adenosine monophosphate (cAMP)-mediated cation channels (HCN1–HCN4, cloned in the late 1990s) in the sinoatrial node. HCN4 is the main isoform in the heart with smaller amounts of HCN1 and HCN2.
physician’s discretion, hoping that large-scale, multicentre, double-blinded, placebo-controlled clinical studies will address this issue.

Conflict of interest: none declared.

References


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Incidental finding of a ruptured thin-cap fibroatheroma by optical coherence tomography

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A 61-year-old male with stable exertional angina presented for elective percutaneous treatment of a left anterior descending (LAD) coronary artery stenosis. Following successful stent deployment, [left coronary angiogram with position of stent demarcated by the two white arrows (Panel A)], optical coherence tomography (OCT) imaging of the LAD artery was performed (LightLab Imaging Inc., Westford, MA, USA). OCT imaging in a region free of significant angiographic stenosis (Panel A, black arrow) revealed a thin-cap fibroatheroma with a ruptured fibrous cap. Panel B shows an OCT image of the plaque with a thin fibrous cap (arrow) measured at 40 μm overlaying a central lipid core (L). Another magnified image of the plaque in Panel D clearly illustrates rupture of the thin fibrous cap (arrow). Intravascular ultrasound imaging at the same position (Panel C) demonstrates the plaque (P), but is unable to distinguish any further morphological detail.