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Review

Heart rate, lifespan, and mortality risk

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ABSTRACT

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. In numerous human studies with patients stratified by resting HR, increased HR is universally associated with greater risk of death. The correlation between HR and maximum lifespan seems to be due to both basal metabolic rate and cardiovascular-related mortality risk. Both intrinsic and extrinsic factors are already postulated to determine how the biological clock works, through regulating and modulating the processes such as protein oxidation, free radical production, inflammation and telomere shortening. Given the remarkable correlation between HR and lifespan, resting HR should be seriously considered as another possible cap on maximum lifespan. Future research is needed to determine whether deliberate cardiac slowing, through methods like lifestyle modification, pharmacological intervention, or medical devices, can decelerate biological clock of aging, reduce cardiovascular mortality and increase maximum lifespan in humans in general.

1. Introduction

Heart rate (HR) is a term used to describe the frequency of the cardiac cycle, which consists of phases of myocardial contraction and relaxation. HR not only reflects the status of the cardiovascular system, but also serves as an indicator of autonomic nervous (sympathetic and parasympathetic/vagal) system activity and metabolic rate. HR is even considered to control the body's metabolic activity (Ferrari et al., 2005). A myriad of factors can affect HR, including but not limited to physical fitness, psychological status, diet, drugs, and the interaction of genetics and the environment. The presence or absence of a pulse, which is equal to HR under normal conditions, was one of the signs that humans learned to use in order to differentiate between life and death thousands of years ago.

Even in modern medicine, HR is one of the vital signs, along with body temperature, respiration and blood pressure (BP). If anything, the importance of HR has been increasingly recognized, as investigations in the recent past have found a new prognostic value for HR, specifically, that higher HR in mammals, including humans, is negatively correlated with lifespan.

This article will review the relationship between basal/resting HR and lifespan and risk of death. It also tries to explore the underlying mechanisms that link HR to lifespan and the possibility of prolonging lifespan through various interventions of cardiac slowing.

2. Heart rate and lifespan in mammals

There is a tremendous amount of variation in HR among homeothermic mammals: 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 (Noujaim et al., 2004). Likewise, mammal lifespan also varies considerably. Mammals that have slower average HR tend to live much longer than those that have faster HR (Levine, 1997; Dawson, 2001). The relationship between HR and lifespan was well presented by Levine (1997), who illustrated that HR is inversely correlated with lifespan in 15 mammal species excluding humans (Fig. 1. See later discussion about human HR and lifespan).

First, let us look at the rodent family, where average HR over 24 h have been measured by radio-telemetry in unrestrained conditions at about 370 bpm in rats (Zhang et al., 2004) and

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Fig. 1. Semi-logarithmic relation between rest heart rate and life expectancy in mammals. Excluding humans, HR is inversely correlated with lifespan in 15 mammal species. Adapted from Levine (1997) with permission.

550 bpm in mice (Zhang, in preparation). Laboratory rats can live for about 3–3.5 years, and mice for about 2–2.5 years. If the total number of heartbeats in the lifetime of both rats and mice are calculated using their average HR, this total number is about 7×10^8 beats in both rodents. This interesting phenomenon can be seen outside the rodent family and in other mammals. Although some variability inevitably exists, calculations using the available data based on observation yield a mean value of around 1×10^9 (1 billion) heartbeats in a lifetime across almost all homeothermic mammals (Fig. 2).

A simplified way to approximately describe this phenomenon is that, on average, mammals have an allotment of 1×10^9 heartbeats, and therefore those who use up their ultimate allotment faster will die sooner.

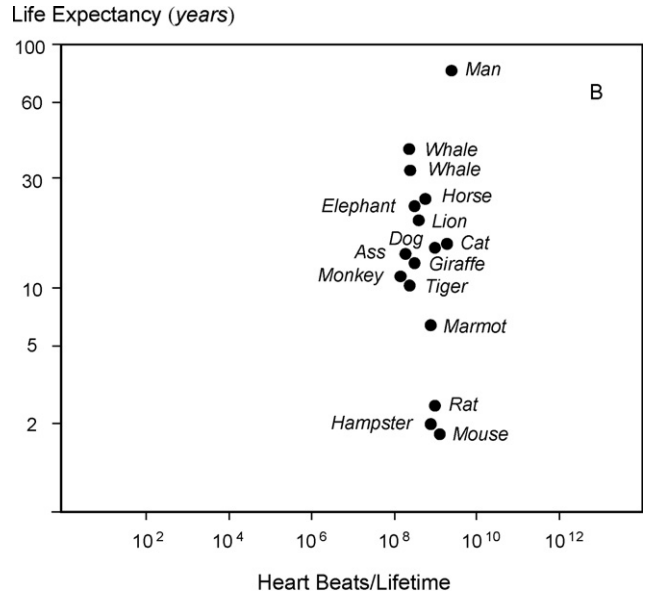

Fig. 2. Total heartbeats over a lifetime of 15 mammal species. The results all fall in a relatively narrow range between 1×10^8 and 3×10^9. Adapted from Levine (1997) with permission.

Given the fact that numerous observational and comparative investigations have established a correlation between HR and lifespan, the idea that there is a predetermined number of heartbeats in a lifetime is not too far-fetched. Cardiac muscle must contract and relax continuously without rest for decades or even more to perfuse organs and tissues in the body with blood (Zhang, 2006). Since cardiac muscle is also unable to regenerate or repair itself, it is not unreasonable to assume that an animal is born with a heart which can only beat so many times before giving out.

Even within the same species, there can be dramatic variations in HR, and the same inverse correlation between average HR and lifespan has been convincing. In humans, for example, several epidemiological investigations have shown that higher HR was strongly associated with cardiovascular mortality or sudden cardiac death (Dyer et al., 1980; Kannel and Schatzkin, 1985; Gillman et al., 1993). In a recent study of exercise and sudden death, it was found that resting HR is positively correlated with death from any cause, and sudden as well as non-sudden death from myocardial infarctions. In this study, the subjects were more closely stratified than in other studies, and even a difference of 15 bpm in resting HR almost doubles the risk of death from any cause and more than triples the risk of sudden death from heart attack (Fig. 3) (Jouven et al., 2005).

It has become recognized that "the predictive power of HR for mortality was higher than that of cholesterol and/or blood pressure" (Palatini et al., 2006a), and some recommendations have been made lately to identify and manage higher HR as an independent risk factor (Palatini et al., 2006a).

There appears to be a gender difference with regard to the prognostic power of HR, as pointed out in a recent review (Palatini et al., 2006b; Fox et al., 2007). For example, studies have shown that women on average live a few years longer than men, but HR in women is slightly faster (Palatini et al., 2002; Bonnemeier et al., 2003). The reason remains largely unknown, and may in fact be coincidental.

Evidently, HR is an independent risk factor, but is not the only one that influences survival duration. Therefore, balanced risk management should target all modifiable risk factors.

When discussing HR and life span measurement in mammals, it has to know that, depending on the source used, a great deal of variability exists. Inevitably, some errors could occur in the measurement of HR because in some (particularly wild) species, HR was only measured in a handful of animals. In addition, many available measurements were made when animals were anesthetized or restrained, so the measured rate is not necessarily the

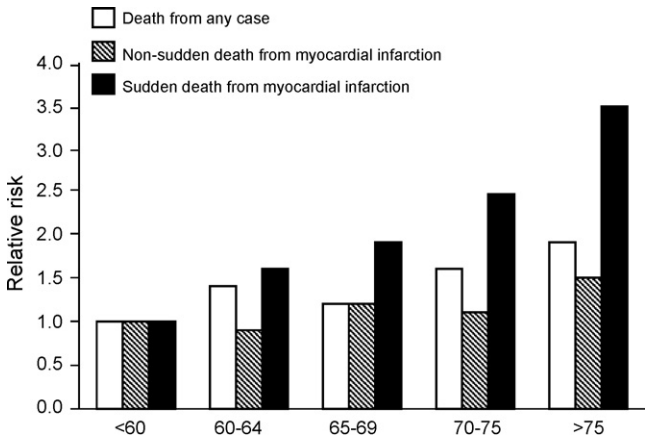

Fig. 3. Correlation between relative risk of death and resting heart rate. Relative risk has been normalized to 1.0 for the <60 bpm group. Adapted from N. Engl. J. Med (Jouven et al., 2005) with permission.

basal HR. Mammal life spans also vary greatly between specimens living in the wild versus captivity. Despite the large variability in animal data, the overall picture depicting the correlation of HR with metabolic rate and life span is quite unambiguous.

3. Are humans significantly different from other mammals in lifespan?

From a diverse sampling of mammals of all sizes, we see that body mass (weight), HR and lifespan are strongly correlated in mammals (Figs. 1 and 2). Very small mammals like mice, rats, and hamsters have the highest HR and lowest life spans. Large mammals like elephants and whales have the slowest heat rates and the longest life spans. Humans, however, represent a distinct outlier in this relationship. Given an average human HR of 60–100 bpm, we should have similar life spans as tigers and giraffes (Zhang, 2006), or about 20 years. As it is, however, our hearts can make about 3×10^9 (3 billion) beats in a lifetime. Why can humans achieve a significantly higher number of heartbeats per lifetime than other mammals? Are humans physiologically or biologically different than other mammals in some way that allows us to "break" the relationship seen in Fig. 1?

The most plausible answer is no, because it has to be pointed out that there are several caveats to the data point representing humans. For a majority of human history, average life span has been less than 30 years (Anon., 2008a) (Fig. 4). A life expectancy of 70–80 years in humans is mainly representative of developed nations in recent decades only. Acquisition of knowledge and development of technology in health care, disease prevention and treatment are primarily responsible for the increase in lifespan in these countries. In the United States, for example, the life expectancy was reportedly below 50 years around 1900, but was close to 80 years in 2007 (Anon., 2008b). Given the fact that life expectancies of 40–50 years is still seen in some countries that lack adequate healthcare and disease control (Anon., 2008b), it is clear that the separation of human lifespan from other mammals (Fig. 1) is largely attributable to acquired knowledge and skills in disease control and prevention, which has drastically lengthened life expectancy over last 1–2 centuries. In modern society, failures in the cardiovascular system are not necessarily fatal; modern medical practices such as cardiopulmonary resuscitation (CPR), defibrillation, pacemakers and many pharmaceutical drugs prolong life and save a great number of people who would have died without intervention.

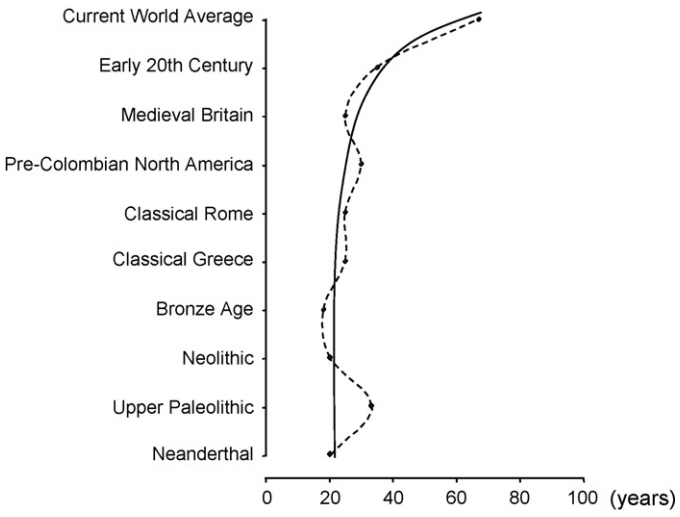

Fig. 4. Life span has increased to over 70 years in 20th century primarily attributed to the advancement in knowledge of healthcare and the development in disease control and prevention. Adapted from http://en.wikipedia.org/wiki/Life_expectancy (Anon., 2008a).

4. Why is faster heart rate correlated with shorter lifespan in mammals?

With the relationship in Figs. 1 and 2 in mind, the overarching questions are (1) why do smaller animals require faster HR and (2) why is faster HR so strongly correlated to shorter lifespan?

One attractive theory to answer the first question is that higher resting HR results from higher basal metabolic rate. High metabolic rate is correlated with body surface area, and because smaller mammals have a greater ratio of body surface area to body weight, they need higher metabolic rates to maintain thermostasis, which is essential for homeostasis in warm blooded mammals (Levine, 1997; West et al., 2002; White and Seymour, 2005).

Oxygen consumption is frequently used as a measure of physical fitness and is a reliable indicator of metabolic activity. Brody, in particular, found relationships between resting HR and average body mass as well as resting HR and the rate of oxygen consumption (VO_2) (Brody, 1945). Interestingly, larger, heavier animals such as elephants have the highest VO_2, but also the lowest HR (Brody, 1945). When normalized by body mass, however, smaller animals have much higher rates of oxygen consumption per kilogram, indicating a faster metabolic rate (Poupa and Brix, 1984).

According to scaling laws, body weight is a variable that determines HR (Dawson, 2001). The relationship is written as

$$HR \propto BW^{1/4}$$

or

$$\mathrm{HR} = C\,\mathrm{BW}^{1/4}$$

where HR is heart rate (bpm), BW is body weight (kg), and C is a coefficient. C varies slightly in the literature, e.g. 241 by Schmidt-Nielsen (1997) and 235 by Noujaim et al. (2004).

Since HR has been shown to be correlated with lifespan, it follows that body weight is correlated with lifespan as well. As Schmidt-Nielsen pointed out in his book, *Animal Physiology: Adaptation and environment*, the average elephant lives 20 times as long as the average mouse because the HR in elephant is 20 times slower (Schmidt-Nielsen, 1997).

To answer the second question, it should be mentioned that a number of epidemiologic studies suggest that a faster HR is associated with development of hypertension, atherosclerosis, sudden death and coronary heart disease, all leading to higher cardiovascular morbidity and mortality (Wilhelmsen et al., 1986b; Palatini, 1999). In the general population, there is a 3-fold increase in mortality in subjects with HR of 90–100 bpm, compared to subjects with HR of less than 60 bpm (Wilhelmsen et al., 1986a), a difference which significantly attributes to increased cardiovascular mortality. In this sense then, HR serves as an indicator of cardiovascular health. In patients with other cardiovascular risk factors, such as hypertension, higher HR can lead to accelerated deterioration of the cardiovascular system. For example, in a 36-year prospective Framingham Study (Fig. 5), increased HR is remarkably correlated with increased incidences of coronary heart disease (CHD), cardiovascular disease (CVD), and mortality from all causes (Gillman et al., 1993). In another well controlled clinical experiment with 2293 elderly men and women, a striking increase in mortality was seen in subjects with resting HR $>$ 79 bpm versus subjects with resting HR $\leq$ 79 bpm (Fig. 6) (Palatini et al., 2002). Similarly, in the Coronary Artery Surgery Study (CASS) registry, a 15-year follow-up of a total of 24,913 patients with suspected or

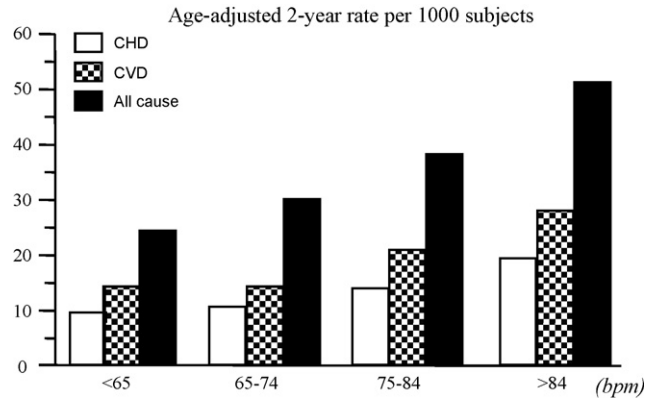

Fig. 5. Association of heart rate with mortality rate among 2037 men with hypertension. Similar trend is seen in women with less mortality rate for each category. CHD, coronary heart disease; CVD, cardiovascular disease. Data from 36-year follow-up of the Framingham Study. Modified from Gillman et al. (1993) with permission.

proven coronary disease, patients with resting HR $\geq$ 83 bpm at baseline had a significantly higher risk for total and cardiovascular mortality than those with HR <62 bpm (Diaz et al., 2005).

In animal experiments, electrical pacing that increases HR is found to stiffen vascular smooth muscle in large arteries, therefore causing progressive and profound reductions in arterial compliance and distensibility (Mangoni et al., 1996; Mircoli et al., 1999). At the molecular level, a 10–20% increase in HR, independent of BP or sympathetic nerve activity (SNA), significantly elevates the level of cardiac nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity and superoxide production, and activates mitogen-activated protein kinases (MAPK), all indicating a greater oxidative stress to the heart and leading to cardiac hypertrophy and fibrosis (Yamamoto et al., 2006). In dogs, increased reactive oxygen species (ROS) are considered to be an important component of the contractile dysfunction following rapid pacing (Gare et al., 2002). Previous studies indicate that the mitochondrial generation rate of ROS plays a significant role in aging and longevity (Barja, 2004; Wolkow and Iser, 2006). Aging is accelerated and longevity is shortened by excessive generation of mitochondrial ROS and the subsequent oxidative damage to mitochondrial DNA and proteins (e.g. telomerase) (Gredilla and Barja, 2005; Partridge and Gems, 2006; Wolkow and Iser, 2006). In laboratory animals, the generation of ROS can be minimized by caloric restriction, which convincingly prolongs lifespan (see Section 5.7) (Gredilla et al., 2001).

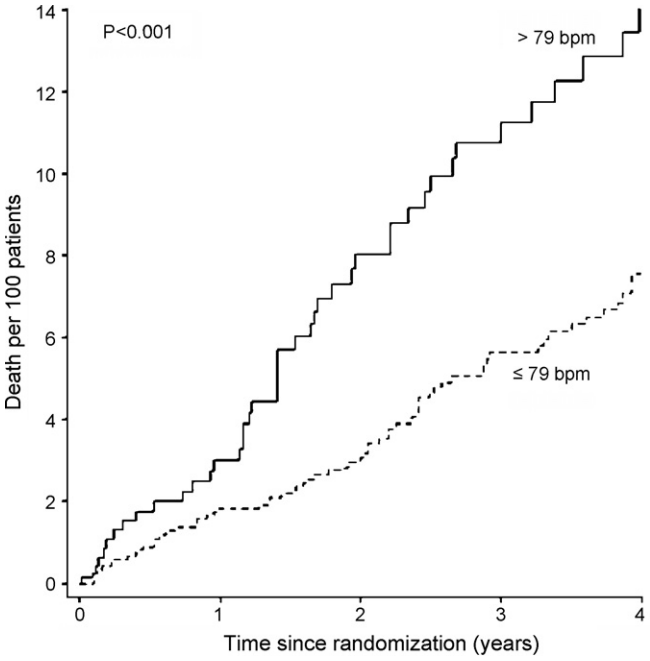

Fig. 6. Kaplan–Meier survival curves for mortality (from all causes) in 2293 elderly men and women with isolated systolic hypertension treated with placebo, stratified by heart rate level. Patients in the top heart rate quintile (>79 bpm) were compared with patients in the four lower quintiles (79 bpm). Adapted from Palatini et al. (2002) with permission from American Medical Association ©2002. All rights reserved.

In addition to the hypothesis of oxidative stress or reactive oxygen species, higher HR is also found to be associated with increased expression of subclinical inflammation molecules, such as interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α) and high sensitivity C-reactive protein (CRP) (Hamaad et al., 2005; Sloan et al., 2007). It has also been shown that the elevation of IL-6 and HR in heart failure patients can be simultaneously reduced by β-blocker treatment (Mayer et al., 2005). Some inflammatory cytokines can increase HR under experimental conditions (Gardiner et al., 1998). HR and biomarkers of inflammation are concurrently reduced by vagal nerve stimulation and by β-adrenergic receptor blockade (Barone et al., 1998; Borovikova et al., 2000; Mayer et al., 2005; Sloan et al., 2007).

Faster basal HR in general represents higher sympathetic tone or a higher ratio of sympathetic/parasympathetic activity. In some disease states, sympathetic activation has been recognized to be of predictive value for poorer clinical outcomes (Benedict et al., 1996; Reuben et al., 2000; Augustyniak et al., 2002).

From a hemodynamic point of view, a slower HR improves ventricular efficiency compared to a faster HR (Burkhoff and Sagawa, 1986; Schoemaker et al., 1998). Unfortunately, in heart failure, HR is actually accelerated due to neurohormonal activation; therefore reducing HR constitutes a therapeutic strategy in improving cardiac insufficiency.

5. Heart rate reduction and its impact on life span

Humans are increasingly approaching an era where cardiovascular health seems to be one of the major upper limits on achievable lifespan. According to the World Health Report 2004, which estimated causes of death in the world in 2002, the leading cause of death in Africa were infectious and parasitic diseases, responsible for over 56% of all deaths (WHO, 2004). On the same continent, HIV/AIDS alone accounted for over 19%, and cardiovascular diseases accounted for just 9.7% of all deaths. In the United States, however, cardiovascular diseases were the leading cause of death, at over 32%, and infectious diseases accounted for merely 6.6% of all deaths. In Europe, cardiovascular diseases accounted for an astonishing 51% of all deaths, and infectious and parasitic diseases accounted for merely 3% of deaths. Clearly, civilization and advances in technology drastically reduce the probability of death by other causes. As the chance of dying to traditional diseases (e.g. infectious disease, malnutrition) becomes increasingly smaller, and as life expectancy continues to rise, it is not unreasonable to assume that more and more people will ultimately succumb to aging related diseases such as cancer, type II diabetes and cardiovascular disease.

Since HR is convincingly correlated with cardiovascular mortality and inversely related to maximum lifespan, the next imperative questions are (1) whether long-lasting basal HR reduction can prolong lifespan and (2) what are the available interventions to reduce HR? While there have been no purposely

designed trials to show that HR reduction by intervention leads to prolonged lifespan in healthy humans, experimental studies in animals and clinical studies in cardiovascular patients have shown some promise. From available literature, the following interventions can achieve negative chronotropic effects.

5.1. HR reduction by β-blocker

One of the indications of β-blockers is to antagonize the action of endogenous catecholamines. When β (type 1) receptors in the sinoatrial (SA) node are occupied by catecholamines, adenylyl cyclase is activated via G protein coupling, which converts ATP to cAMP. cAMP accelerates spontaneous diastolic depolarization of the pacemaker cells through at least two major mechanisms: first, it augments Ca^{2+} current, allowing more calcium into the cell. The calcium channels open more easily with depolarization, which increases the rate of spontaneous diastolic depolarization; second, it augments a mixed Na^+–K^+ inward current by opening hyperpolarization-activated channels (i.e., funny channel or f-channel. See Section 5.3) that also control the rate of the depolarization. β-blockers interrupt this β-adrenergic signaling cascade at the receptor level, therefore reducing cAMP availability and the opening probability of these ion channels, leading to a decrease in HR.

After being contraindicated in chronic heart failure for almost 30 years, β-blockers, given on top of standard therapy, have been proven to further reduce mortality and morbidity over last two decades (Funck-Brentano, 2006). Data analysis of clinical trials has unequivocally ascribed the reduction of cardiovascular mortality, sudden cardiac death, hospitalizations, death due to progression of heart failure, and improved NYHA functional class to the negative chronotropic effect of β-blockers. Interestingly enough, further analysis also reveal that patients who benefited most from β-blocker regimen were those who had higher basal HR and greater HR reduction on the regimen (Kjekshus, 1986; Packer et al., 1996; Huang et al., 2006). Recently, in patients with symptomatic and systolic left ventricular function who were pacemaker dependent and on β-blockers, these subjects with the lower pacing rate of 60 beats per minute had improved ejection fraction and left ventricular volume more significantly than those with the higher pacing rate of 80 beats per minute (Thackray et al., 2006).It should be mentioned that unlike heart failure trials, clinical antihypertension trials that lasted ~4–6 years on average have not found that the negative chronotropic property of β-blockers makes them superior to other classes of antihypertensive agents in term of reducing cardiovascular morbidity and mortality (Anon., 1992; Dahlof et al., 2002). This is possibly unrelated to the negative chronotropic effect of β-blockers, but rather due to the deteriorated metabolic profile (worsening glucose tolerance and onset of diabetes) associated with β-blocker regimen.

5.2. HR reduction by calcium channel blocker

Dihydropyridine CCBs, particularly the short-acting ones, fall short of expectations in secondary prevention, putatively because when they cause direct vasodilatation they provoke a series of reflexive neurohormonal responses, such as sympathetic activation and tachycardia (Zhang, 1996; Zhang and Wang, 2001). On the other hand, non-dihydropyridine CCB, mainly phenylalkylamines (e.g. verapamil) and benzothiazepines (e.g. diltiazem), are negative chronotropes with antihypertensive and antiarrhythmic effects (Zhang, 1996; Papadopoulos and Papademetriou, 2008). By blocking L-type channels in pacemaker cells, verapamil and diltiazem slow depolarization and action potential propagation, which are dependent on inward calcium current. Moreover, they may also slow HR through sympathetic suppression (Kailasam et al., 1995; Binggeli et al., 2002). Unlike dihydropyridine CCBs that cause reflex tachycardia, non-dihydropyridine CCBs reduce HR. In patients post-acute myocardial infarction without heart failure, verapamil reduced cardiovascular morbidity and mortality (Anon., 1990). HR reduction by verapamil and diltiazem causes a negative inotropic effect, which limits their use in patients with heart failure or patients with pulmonary congestion (Messerli et al., 2001).

5.3. HR reduction by f-channel blocker

This is a class of drugs that act inhibitively and exclusively on the funny (f)-channels. f-channels turn off during upstroke of an action potential and turn on when repolarization reaches between −40 and −50 mV during phase 4. The opening of f-channels is accompanied by slow inward current I_f, which is an inward movement of sodium and potassium ions. I_f antagonizes the hyperpolarizing effect of the outward current I_k until maximum diastolic potential is reached, and allows spontaneous diastolic depolarization by influx of more sodium and potassium ions until the threshold is reached for fast inward current activation (Ca^{2+}-current) to trigger a new action potential (DiFrancesco, 2006a,b). cAMP binds f-channels and has been shown to be a second messenger in modulating I_f: increased cAMP production (i.e., sympathetic activation. See Section 5.1) results in more inward current and a consequent acceleration of depolarization slope and rate; whereas decreased cAMP availability (i.e., parasympathetic activation) results in less inward current and a negative chronotropic effect on HR (DiFrancesco, 2006a,b).

In the circulatory system f-channels are found exclusively in pacemaker cells, which is a downstream HR regulation mechanism—its blockade is normally without other cardiovascular effects. Compared with β-blockers and CCBs, which produce negative inotropic effects, alter vascular resistance, and reduce BP, I_f inhibitors e.g. ivabradine appear to be an ideal drug for investigating pure HR effects on lifespan.

Clinically, the negative chronotropic effect of ivabradine is well established for preventing angina pectoris (Borer, 2006). Animal studies have also shown that HR reduction by ivabradine in heart failure rats is accompanied by reduced left ventricular end systolic diameter, decreased collagen density and increased capillary density of the left ventricle (Mulder et al., 2004). A clinical trial to assess whether ivabradine lowers mortality and morbidity is currently underway (Fox et al., 2006).

5.4. HR reduction by digoxin

Digoxin is an important cardiac glycoside that enhances myocardial contractility and lowers HR. By inhibiting Na^+/K^+ ATPase pump of the pacemaker cells in the SA node, digoxin increases intracellular sodium level, which reduces efflux of calcium by sodium gradient-dependent Na^+/Ca^{2+} exchange pump. As a result, the length of phase 4 and phase 0 of the cardiac action potential is prolonged. Digoxin also decreases the conduction of electrical impulses through the atrioventricular (AV) node and has parasympathetic mimetic effect. All of these lead to slower rate of pacemaking.

In 1970s, Coburn et al. published experimental reports that demonstrated that digoxin, fed from weaning to death, had significant effects on lifespan in A/J mice. In untreated animals the mean HR was 526 bpm; in treated it was 270 bpm. Accordingly, the mean lifespan in untreated males was 575 days, untreated females 752 days; treated males 741, treated females 858 days (Coburn et al., 1971). However, despite equal caloric intake, the treated mice had lower body weights than untreated mice (Coburn et al.,

1971). It is unknown whether the retarded growth might have also played a role in prolonging the survival time in treated mice. Clinically, digoxin is used to control supraventricular tachycardia, particularly atrial fibrillation and to improve left ventricular function in heart failure, in which HR reduction plays a key role. Although digoxin has a narrower safety margin between hemodynamic/symptomtic effective and toxic doses, recent studies show that it is possible to improve survival rate by achieving a lower serum digoxin concentration (0.5–0.9 ng/ml) in human heart failure patients (Gheorghiade et al., 1995; Newton et al., 1996; Slatton et al., 1997; Adams et al., 2002; Ahmed et al., 2006).

5.5. HR reduction by vagal nerve stimulation (VNS)

The most remarkable effect of efferent VNS is bradycardia, via activation of muscarine receptor (type 2) by acetylcholine (ACh)—the principal neurotransmitter of the vagal efferent nerve endings. Unlike β receptors, the activation of muscarinic receptors is negatively coupled with adenylyl cyclase, which in turn, reduces cAMP formation, inactivates f-channels and reduces current I_f (see Sections 5.1 and 5.3).

In heart failure rats, a targeted reduction of HR by 20–30 bpm with electrical VNS for 6 weeks, started 2 weeks post-myocardial infarction, significantly improved both cardiac hemodynamic and remodeling profiles (dp/dt increased, LVEDP decreased and ventricular hypertrophy attenuated) (Li et al., 2004). The 6-week VNS even resulted in improvements of long-term survival rate: without active treatment, 50% of the rats died at 20 weeks post-myocardial infarction (LCt_{50} = 20 weeks), whereas only 10% of the rats that received the stimulation died during the same period.

One pathophysiological characteristic of human and animal heart failure is sympathetic activation, as seen by direct recording of SNA, or by measurement of plasma catecholamine concentration (Benedict et al., 1996; Zhang et al., 1997, 1999, 2004). Increased sympathetic activity is a risk factor for future cardiovascular events, as it promotes cardiac hypertrophy and fibrosis, and potentiates the renin–angiotensin system (Francis, 1989; Zhang et al., 1999; Teisman et al., 2000), in addition to its hemodynamic effects. By elevating vagal tone, VNS (and borareceptor stimulation, which is discussed later) exerts anti-sympathetic action through two major mechanisms (Kalsner and Quillan, 1988; Giessler et al., 1999). First, it inhibits myocardial presynaptic norepinephrine release, therefore reducing catecholamine concentration at the neuromuscular junction and subsequently in the systemic circulation. Second, it suppresses cAMP production in response to β-adrenergic signaling cascade through G-protein, therefore slowing the spontaneous diastolic depolarization in SA node, which is controlled by f-channels (Renaudon et al., 1997).

Other than negative chronotropic and anti-sympathetic effects, the cholinergic effect of vagal activation also mediates anti-inflammatory actions. For example, the release of some inflammatory cytokines including TNF-α, IL-1β, IL-6, and IL-18 in lipopolysaccharide-stimulated human macrophage culture were suppressed *in vitro* by ACh (Borovikova et al., 2000). In an endotoxemic shock model induced by lipopolysaccharide (Gidlof et al., 2000), bilateral VNS prevented BP from collapsing and plasma TNF-α from surging (Borovikova et al., 2000). Interestingly, a number of these cytokines can actually cause tachycardia which is not baroreceptor reflex mediated, as the tachycardia effect appeared to precede the hypotensive effect (Borovikova et al., 2000). More importantly, ACh release during VNS activates the classical pathway of endothelial dependent nitric oxide synthesis, an essential and constitutive cardiovascular protective mechanism against hypertension, atherosclerosis and coronary events (Thomas et al., 2001; Augustyniak et al., 2005).

Conventional VNS may activate both efferent and afferent fibers; newer technology has been developed to selectively stimulate efferents in the vagus. Recent preclinical experiments show that 3-month selective stimulation improves LV function and attenuates LV remodeling in dogs with microembolization-induced heart failure, together with normalization of TNF-α, IL-6 and NT-ProBNP (Gupta et al., 2006a), nitric oxide mRNA and protein expression (Gupta et al., 2006b). VNS is now in testing for human subjects with heart failure.

5.6. HR reduction by baroreceptor stimulation

The baroreceptor reflex is a negative feedback system that works primarily in response to fluctuations in BP. Artificial simulation of baroreceptor afferent nerves make the brain think that BP is actually elevated, resulting in a coordinating process in the vasomotor center located in the brain stem. The subsequent response to the artificial baroreceptor activation is an increase of parasympathetic outflow (see Section 5.5) and a decrease of sympathetic outflow to the heart and blood vessels. The difference between baroreceptor stimulation and vagal efferent stimulation is that the latter is usually not accompanied by BP change. In other words, baroreceptor stimulation decreases not only HR but also BP because of vasodilatation (Mohaupt et al., 2007; Sloand et al., 2007).

5.7. HR reduction by reduced energy intake

As early as in 1935, it was reported that caloric restriction (CR) increased lifespan in rodents (MaCay et al., 1935). Over last 70 years, the same finding has been repeatedly confirmed, and numerous studies report that CR increases lifespan and delays the occurrence of pathophysiological changes in various mammalian species, including non-human primates (Weindruch and Sohal, 1997; Mattison et al., 2003). CR by 40% reduces HR by ~10% and diastolic arterial pressure by ~10 mmHg (Mager et al., 2006). Later studies have also found that CR and intermittent fasting can (1) change the balance of sympathetic and parasympathetic nervous system, thus decreasing BP and HR (Mattson and Wan, 2005; Mager et al., 2006); (2) reduce ROS production and its damage on mitochondria (Gredilla et al., 2001); and (3) improve insulin sensitivity. Again, like some methods discussed above, CR does not solely affect HR, so it is unlikely that HR reduction alone explains all the results observed in these studies.

Several mechanisms have been proposed to be related to the beneficial lifespan-extending and anti-aging effects of calorie restriction at the cellular level (Gredilla et al., 2001; Mattson and Wan, 2005; Ungvari et al., 2008). Mainly, it reduces free radical generation and inflammation gene expression and prevents oxidative stress; it also increases resistance against cellular stress, by upregulating the expression of some heat shock proteins (Hall et al., 2000; Koubova and Guarente, 2003; Yan et al., 2007) and maintains genomic integrity by telomerase and DNA repair proteins (Mattson et al., 2002; Kenyon, 2005).

5.8. HR reduction by physical exercise

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 (Carter et al., 2003). While exercise itself elevates HR significantly, resting HR is significantly reduced and overall total heartbeats over 24 h are reduced as well. For example, in a recent 6-week study of 21-year-old subjects, exercise was found to have a significant effect on resting HR. In the exercise group, baseline resting HR was 68 bpm, and after 6 weeks of cycling

exercises of 40 min/day at 80% peak VO_2 the resting HR was 53 bpm. In the control group with no exercise, the baseline resting HR was 68 bpm, and 66 bpm after 6 weeks (Yamamoto et al., 2001). Long-term endurance training also decreases submaximal exercise HR by reducing sympathetic activity to the heart (Carter et al., 2003). In a randomized study to compare the effects of a 12 months exercise training program versus standard percutaneous coronary intervention (PCI) with stent, resting HR was reduced by 6 bpm (from 71 at baseline to 65 bpm at end of the study) in the active exercise group and remained same in PCI group (from 70 at baseline to 70 bpm at end of the study), which was associated with a higher event-free survival rate (88% vs. 70%) and increased maximal oxygen uptake (Hambrecht et al., 2004). Regular moderate exercise improves endothelial function and reduces oxidative stress, therefore augmenting nitric oxide pathway (Thomas et al., 2001; Augustyniak et al., 2005; Radak et al., 2008).

It should be pointed out that regular endurance exercise brings out many other physiological changes in addition to reduced resting HR, such as increased lung capacity, muscle mass, reduced cholesterol level, increased baroreflex sensitivity and decreased BP (Cornelissen and Fagard, 2005). Moreover, from a practical standpoint, HR reduction by exercise and CR is less costly compared to pharmaceutical agents or medical devices.

The pharmacological and medical device interventions discussed above are currently for patients with cardiovascular disease. For healthy subjects, lifestyle modification such as regular and moderate exercise, energy intake control and fish oil consumption (Mori et al., 1999) appears to be the more appropriate approach at the moment.

6. Conclusion

Recent research has uncovered increasing evidence that HR is inversely related to the lifespan among homeothermic mammals and among individual species. There already exist numerous factors which are postulated to determine maximum lifespan, including protein oxidation, free radical production, and telomere shortening. Given the remarkable correlation between HR and lifespan, resting HR should be seriously considered as another possible cap on maximum lifespan. The correlation between HR and maximum lifespan seems to be determined by both metabolic rate and cardiovascular-related mortality risk. More research is needed to determine whether cardiac slowing intervention by modifying lifestyle, by pharmacological products or by medical devices can increase maximum lifespan. It is interesting to note that lifestyle factors commonly recognized as healthy, such as stress avoidance, caloric restriction, and regular exercise are all methods which can result in resting HR reduction, but whether the health benefits are due to HR reduction alone are unclear. In the absence of data from purely bradycardiac drug, the exact effects of HR reduction in humans are difficult to ascertain. In numerous studies with patients stratified by resting HR, however, increased HR is universally associated with greater risk of death. As such, HR serves as a clear and accurate indicator and predictor of cardiovascular health and mortality. Cardiovascular disease is now one of the leading causes of death in the world, and further efforts in this area, including research, prevention, and treatment from heart rate perspective, should be prioritized.

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