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Heart Rate, Life Expectancy and the Cardiovascular System: Therapeutic Considerations

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Key Words
Heart rate · Cardiovascular system · Life expectancy

Abstract
It has long been known that life span is inversely related to resting heart rate in most organisms. This association between heart rate and survival has been attributed to the metabolic rate, which is greater in smaller animals and is directly associated with heart rate. Studies have shown that heart rate is related to survival in apparently healthy individuals and in patients with different underlying cardiovascular diseases. A decrease in heart rate due to therapeutic interventions may result in an increase in survival. However, there are many factors regulating heart rate, and it is quite plausible that these may independently affect life expectancy. Nonetheless, a fast heart rate itself affects the cardiovascular system in multiple ways (it increases ventricular work, myocardial oxygen consumption, endothelial stress, aortic/arterial stiffness, decreases myocardial oxygen supply, other) which, in turn, may affect survival. In this brief review, the effects of heart rate on the heart, arterial system and survival will be discussed.

Introduction

It has long been known that resting heart rate is inversely related to average life span in most organisms that have been studied. Indeed, among mammals, where the relationship has been most intensively assessed, there is a linear, inverse semilogarithmic relationship between average resting heart rate and average life expectancy in all species except humans (who live longer than is predicted from their heart rate). This observation presumably relates to the interposition of medical care [1, 2] (fig. 1). The association between heart rate and life expectancy has been attributed to the metabolic rate, which is greater in smaller animals and is directly associated with heart rate. However, there are many other factors that affect heart rate, such as genetic influences on the cell biology of electrically active atrial tissues, autonomic nervous activity, inflammatory processes, etc. It is possible that the same factors that influence heart rate may also independently affect life expectancy. Nonetheless, heart rate itself affects the cardiovascular system in multiple ways that possibly influence survival. Consequently, heart rate may contribute to the development and accel-

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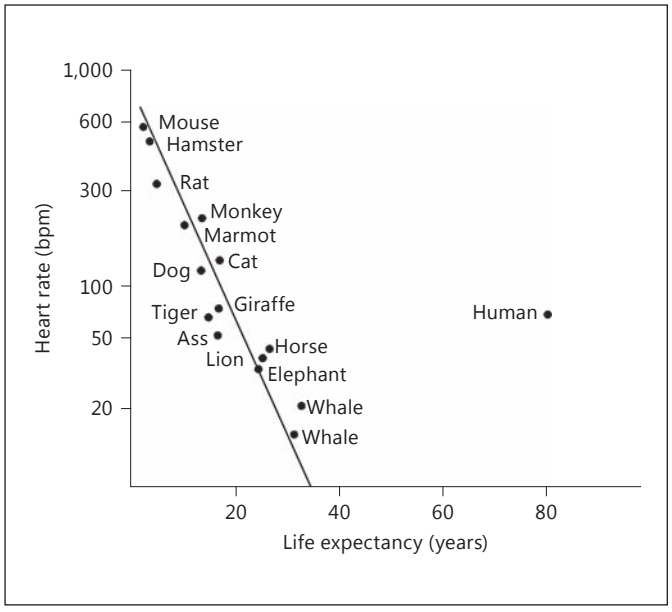

Fig. 1. Semilogarithmic relation between resting heart rate and life expectancy in mammals [1].

eration of certain cardiovascular diseases, that, in turn, affect life expectancy [1–6]. In this brief review, the effects of heart rate on the heart, arterial system and survival will be considered.

Effects of Heart Rate on the Heart

Conventionally, heart rates of 50 or 55–90 beats per minute (bpm) at rest are considered normal, but in fact, due to the wide variability of heart rate at different times of the day in relation to different activities and also to intercurrent diseases, it is difficult to precisely define the range for normal heart rate [1, 2, 7]. For example, the normal heart rate is typically much slower at night than during the day and, as a general rule, slightly faster in women than in men.

Heart Rate, Ventricular Work and Coronary Flow

Ventricular work and myocardial oxygen consumption (MVO_2) are directly related to heart rate. As heart rate increases, the supply of myocardial oxygen diminishes, because the diastolic time interval during which myocardial blood flow occurs decreases relatively rapidly as heart rate increases [7]. Diastolic time is an especially important factor when left ventricular (LV) hypertrophy and/or coronary artery disease are present. LV intramyocardial pressure during systole is equal to or greater than LV systolic pressure in the subendocardium. In patients with hemodynamically important obstructive coronary artery disease, systolic flow may be obliterated because the coronary systolic pressure distal to an obstructive lesion is less than the LV wall pressure during systole. Therefore, subendocardial blood flow, collateral flow and flow distal to an obstruction become dependent on the duration of diastole (fig. 2a). Ventricular filling also occurs during diastole. At fast heart rates, the ventricular filling time (i.e. diastolic time) shortens dramatically, left atrial pressure increases and pulmonary edema may occur. Irregular heart beat also alters the expression and activity of key proteins, regulating calcium turnover within the myocardial cells that may decrease myocardial contractility [7–15].

Heart Rate and Diastolic Time

Diastolic time has a nonlinear relationship to heart rate. Thus, small changes in heart rate, especially when <75 bpm, will produce a disproportionate increase in diastolic time (fig. 2b). In contrast, the relationship between heart rate and duration of systole is linear. Although the duration of systole changes according to heart rate, these changes are small and substantially fewer than the changes that occur in diastolic time [7]. The effects of heart rate on the heart are summarized in table 1.

Effects of Heart Rate on the Arterial System

Heart Rate and Endothelial Function

LV systole results in a generation of pressure that travels from the root of the aorta into the peripheral arterial circulation as a pulse wave [16–19]. The pressure waves with each ventricular systole produce a stress on the arterial endothelial cells. Intrinsic repair mechanisms maintain normal endothelial function when the applied stress is within physiologic limits. When the stress is pathologic (e.g. high arterial pressure or in the presence of other risk factors such as smoking, high levels of cholesterol, inflammatory process, aging, etc.) the intrinsic repair mechanisms are inadequate to maintain normal endothelium, and thus endothelial damage may occur. This may result in arterial aging and cardiovascular disease. The faster the heart rate, the greater the effect on the endothelium. In fact, endothelial damage and repair starts in utero with the first heart beat [20, 21].

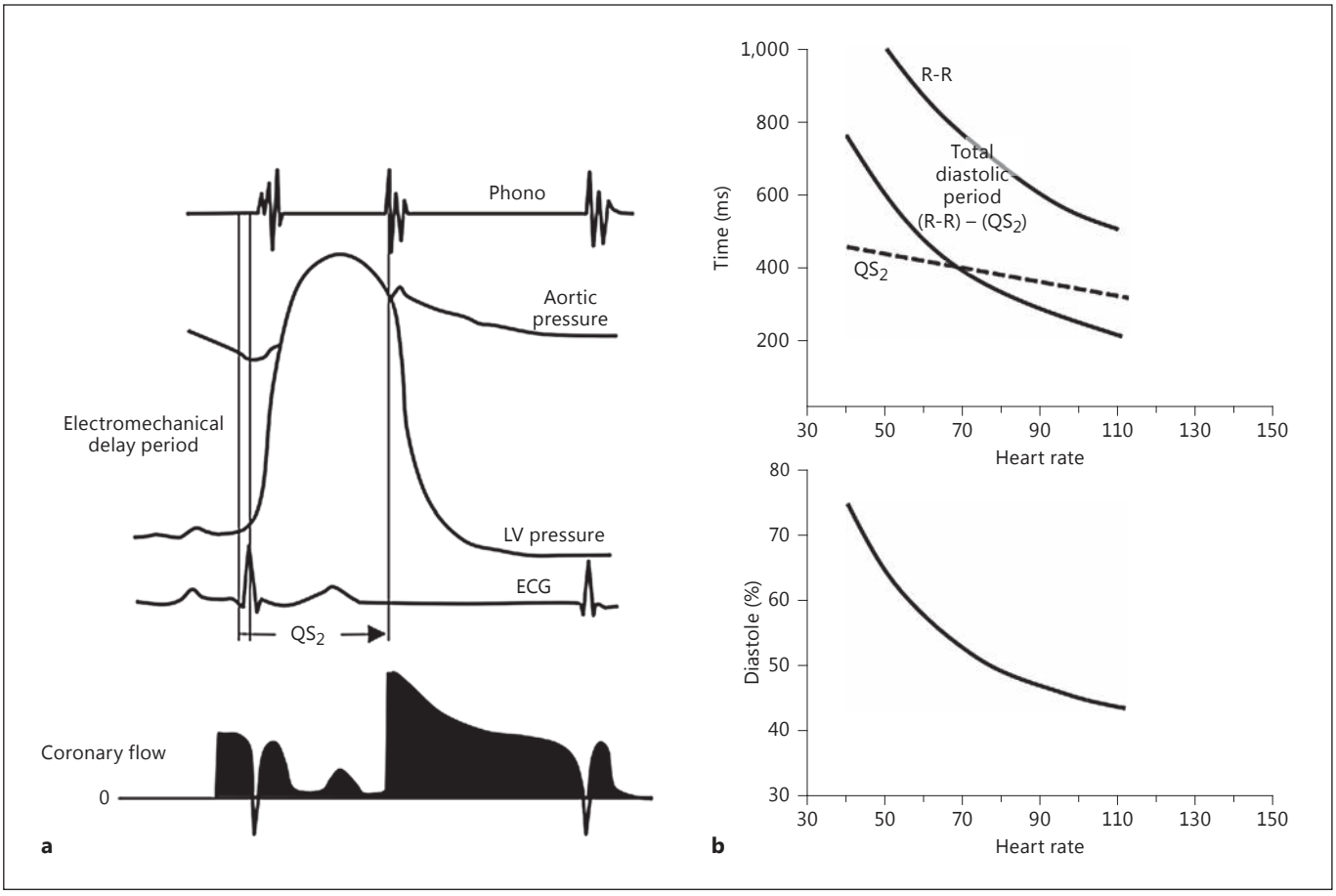

Fig. 2. a Schematic presentation of coronary flow in relation to the cardiac cycle. Note that the greater proportion of coronary flow occurs in diastole. Left ventricular (LV) work is related to the duration of systole and LV systolic pressure. First and second heart sounds, and the electrocardiogram (ECG) are also shown [11]. **b** Upper panel: relationship between heart rate, total electromechanical systole, i.e. systolic time, relative risk interval and diastolic period. Two factors determine the duration of diastolic time: heart rate and the duration of systole. Lower panel: relationship between heart rate and percent diastole. Due to a nonlinear relationship, small changes in heart rate produce dramatic changes in diastolic time, especially at a slower heart rate. The relationship between the systolic time and heart rate is linear, thus changes in heart rate produce substantially smaller changes in systolic versus diastolic times [7]. QS_2 = Systolic time; R-R = relative risk.

Heart Rate, Arterial and Aortic Function

Faster heart rates also result in arterial stiffening. Increasing the rate by pacing from 60 to 90 bpm in humans results in a decrease in carotid and radial artery distensibility. In experimental animals, an increase in heart rate results in stiffening of the aorta. A fast heart rate is also a major determinant of accelerated progression of aortic stiffness in treated patients with arterial hypertension [21–27]. A stiff aorta will increase the aortic pulse wave velocity (PWV). Increased PWV results in rapid expansion of the arterioles and damage to organs, especially the kidneys and the brain (fig. 3a). A stiff aorta will also increase reflected wave velocity. Normally reflected waves

Table 1. Effects of fast heart rate on the heart

- ↓ Diastolic time
  - ↓ Myocardial blood flow
  - ↓ Ventricular filling time (functional mitral stenosis)
- ↑ Systolic time
  - ↑ Ventricular work
  - ↑ Myocardial oxygen consumption (MVO_2)
- Irregular heart rhythm may alter the expression and activity of key calcium-handling proteins
- Other

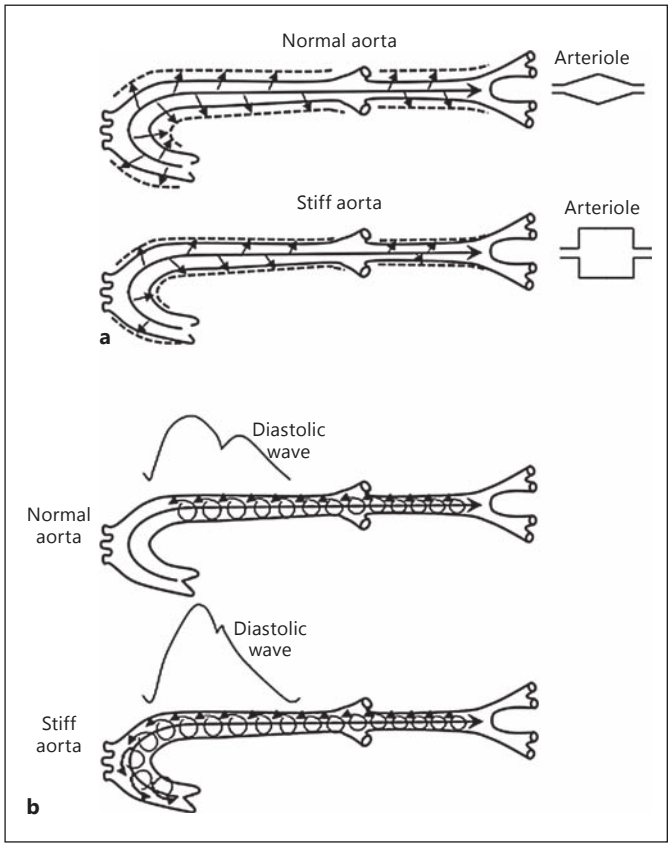

Fig. 3. a Pulse wave velocity (PWV) is shown schematically with large arrows. When the aorta is stiff, PWV increases, resulting in stretching of the peripheral arterioles and vascular damage. **b** Reflected wave velocity in a stiff aorta is faster than in a normal aorta, so reflected waves reach the root of the aorta at the end of systole; this results in an increase in the systolic pressure and the disappearance of the diastolic wave. The pulse pressure waves of the carotid artery or the central aorta in both a normal and a stiff aorta are also shown schematically (see text for detail) [18].

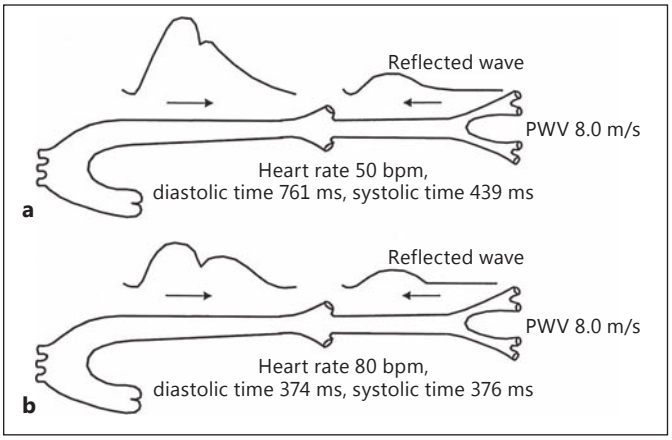

Fig. 4. a Slow heart rate may result in an increase in central aortic pressure due to a significant increase in diastolic time compared to an aorta with the same length and the same elastic properties, but a normal heart rate. **b** Note that diastolic time increased from 374 to 761 ms but systolic time increased only to 439 from 376 ms when the heart rate decreases from 80 to 50 bpm. The central aortic pressure waves with a heart rate of 80 or 50 bpm are also shown schematically (see text for detail). PWV = Pulse wave velocity.

arrive in the root of the aorta early in diastole and form the diastolic wave, which facilitates coronary blood flow. When reflected wave velocity is increased, reflected waves arrive in the root of the aorta late in systole. The result is the disappearance of the diastolic wave and an increase in the systolic pressure, producing an increase in LV work, MVO_2 and reduced coronary blood flow [16–19] (fig. 3b).

Heart Rate and Central Aortic Pressure

When the heart rate is relatively slow, reflected waves may reach the root of the aorta in systole even if the elastic properties of the aorta are normal. This may result in an increase in the central aortic pressure (fig. 4). Thus, when the heart rate slows sufficiently, the central aortic pressure will increase, assuming that the aortic function remains unchanged. When the aortic function improves and the heart rate decreases, as with regular aerobic exercise, the central aortic pressure may stay the same, despite a slower heart rate. In contrast, when the heart rate decreases with pharmacologic agents that do not alter aortic function, as with β-adrenergic blocking agents, central aortic pressure may increase. This is not related to an increase in the duration of systole, as previous investigators suggested, but mostly to an increase in the duration of diastole. The effect of a slow heart rate on the central aortic pressure may be enhanced when a slow heart rate is associated with an increase in peripheral resistance [16–19, 21–24].

Other Abnormalities Associated with Fast Heart Rates

Faster heart rates are also associated with other abnormalities such as inflammatory processes, oxidative stress and endothelial dysfunction that may accelerate atherosclerosis. A fast heart rate at rest is associated with increased sympathetic activity and decreased heart rate variability, which are associated with cardiovascular mortality. As heart rate increases, the likelihood of microal-

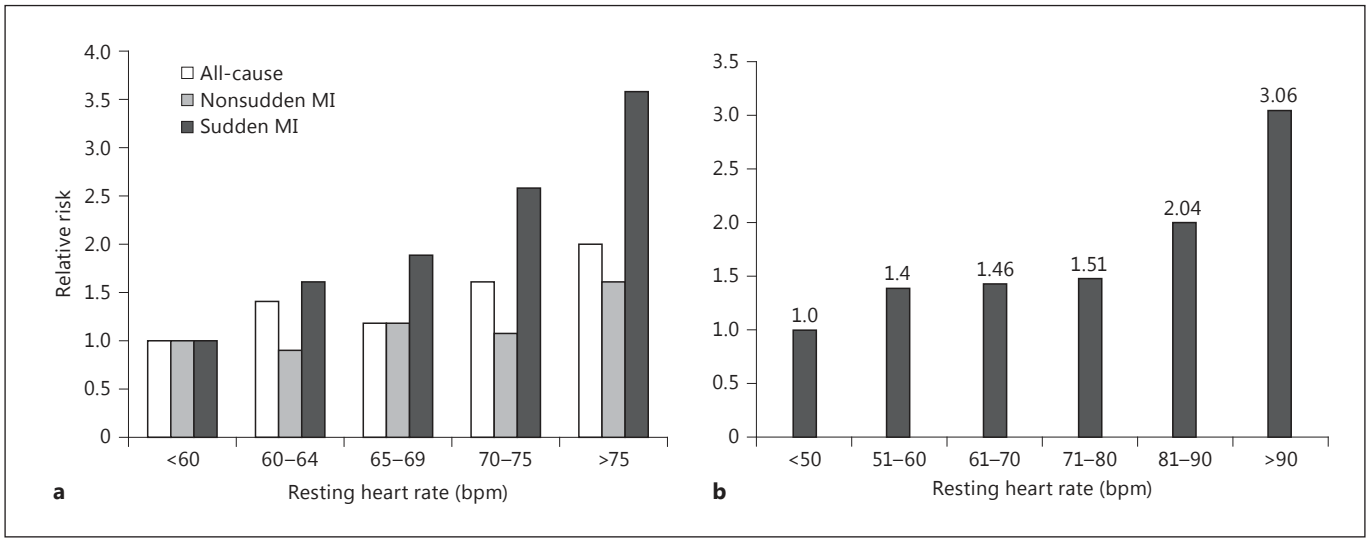

Fig. 5. a Relative risk of death from any cause, sudden death and nonsudden death due to myocardial infarction (MI) in relation to resting heart rate in healthy men [34]. **b** All-cause mortality in relation to resting heart rate adjusted for age, physical activity, fitness, maximal myocardial oxygen consumption (MVO_2 max), leisure time, tobacco consumption, alcohol intake, body mass index, systolic/diastolic pressure, serum cholesterol and triglycerides (constructed using data from [35]).

buminuria also increases in patients with diabetes mellitus and arterial hypertension [28–33]. Importantly, these associations between heart rate and various cardiovascular abnormalities do not necessarily indicate a direct causal relation. The intervening pathophysiology requires further study.

Association between Heart Rate and Survival

Heart Rate and Mortality in Apparently Healthy Individuals

In numerous epidemiologic studies, cardiovascular and all-cause mortality in healthy individuals has been directly related to heart rate. For example, in a 23-year follow-up of 5,713 asymptomatic men (age range 32–42 years) without clinical evidence of underlying cardiovascular disease, the risk of sudden death from myocardial infarction was higher in subjects with a resting heart rate >75 bpm at study entry than among those with a lower entry heart rate [34] (fig. 5a). In the more recent Copenhagen Male Study, 2,978 subjects in sinus rhythm without known cardiovascular disease or diabetes mellitus were followed for 16 years [35]. Again, heart rate was directly associated with mortality, beginning with rates exceeding 55 bpm (fig. 5b). The relationship between heart rate and mortality persisted even after adjustment for physical activity, fitness, maximal MVO_2, smoking, leisure time, alcohol intake, body mass index, systolic and diastolic blood pressure, and levels of serum cholesterol and triglycerides.

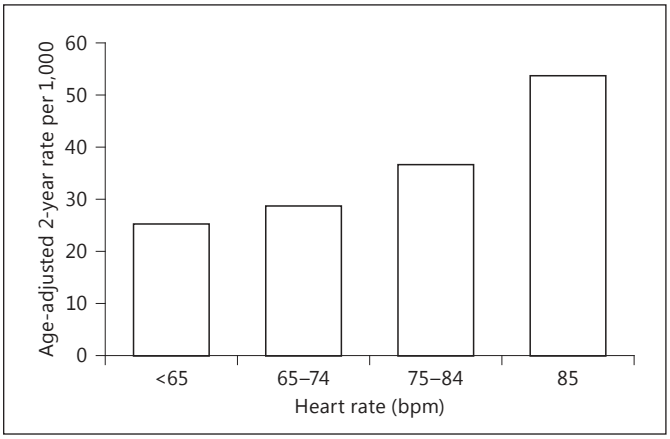

Fig. 6. Resting heart rate as a predictor of all-cause mortality in patients with arterial hypertension in the Framingham Study, which included 2,037 men with a 36-year follow-up.

Heart Rate and Mortality in Arterial Hypertension

The Framingham study [36] evaluated 4,530 patients with arterial hypertension aged 34–74 years whose blood

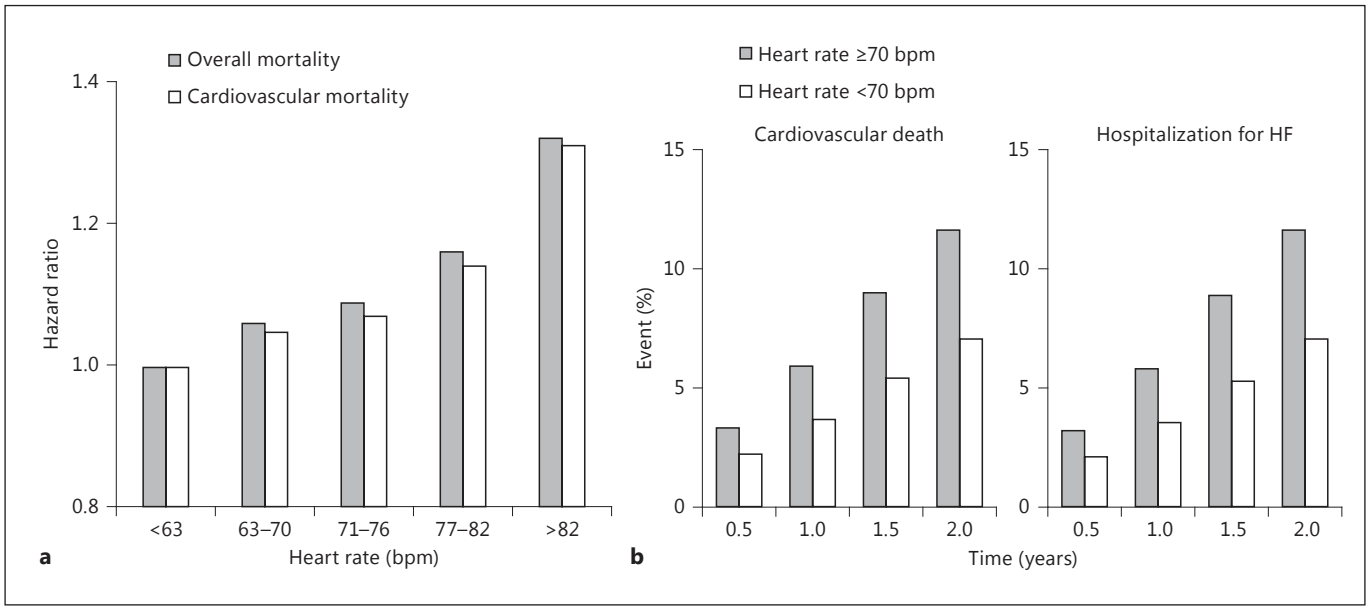

Fig. 7. a Mortality in relation to resting heart rate in coronary artery disease adjusted for age, gender, hypertension, diabetes mellitus, cigarette smoking, clinically significant coronary artery disease, left ventricular (LV) ejection fraction, recreational activity and treatment with antiplatelets, diuretics, β-blockers and lipid-lowering drugs (modified from [40]). **b** Heart rate as a predictor of cardiovascular events and hospitalization for heart failure (HF) in patients with coronary artery disease and LV systolic dysfunction. Note that cardiovascular death and hospitalization for heart failure were greater in those with a heart rate ≥70 bpm than in those with a heart rate <70 bpm [41].

pressure was ≥140 mm Hg systolic or ≥90 mm Hg diastolic, and were not treated with antihypertensive medications at baseline. After 36 years of follow-up, all-cause mortality was directly related to resting heart rate at study entry [36–39] (fig. 6).

Heart Rate and Mortality in Coronary Artery Disease

The relationship between resting heart rate at baseline and cardiovascular mortality/morbidity was assessed in 24,913 patients with suspected or proven coronary artery disease in the Coronary Artery Registry, established along with the CASS (Coronary Artery Surgery Study [40]), for a median follow-up of 14.7 years. Overall mortality and cardiovascular mortality increased with increasing baseline heart rate (fig. 7a). Heart rate as a prognostic factor for patients with coronary artery disease and LV systolic dysfunction was evaluated in the placebo group of the prospective, placebo-controlled, randomized BEAUTIFUL (Morbidity-Mortality Evaluation of the I(f) Inhibitor Ivabradine in Patients with Coronary Disease and Left Ventricular Dysfunction) trial. The 5,438 placebo-treated patients (heart rate ≥60 bpm) were prospectively dichotomized into a group with a heart rate ≥70 bpm (n = 2,693) and a group with a heart rate <70 bpm (n = 2,745). Those with a rate ≥70 bpm at entry had significant more cardiovascular events (cardiovascular death, admission for heart failure, myocardial infarction and myocardial revascularization) during the average 19-month follow-up than those with a rate <70 bpm [41] (fig. 7b).

Heart Rate and Survival after Therapeutic Interventions

Patients with Coronary Artery Disease

It is known that therapy with β-adrenergic blocking agents, when begun shortly after acute myocardial infarction, decreases mortality [42, 43]. In a large, prospective, randomized, double-blind trial, the difference in heart rate between the groups treated with β-blockers and the placebo groups was directly related to the reduction in mortality [42] (fig. 8a). In another trial, the same relationship was found between a reduction in heart rate in the treatment group and nonfatal myocardial infarction [43]. These associations between heart rate and mortality or myocardial infarction are at least partially related to the decrease in LV work and MVO_2 and to an increase in the

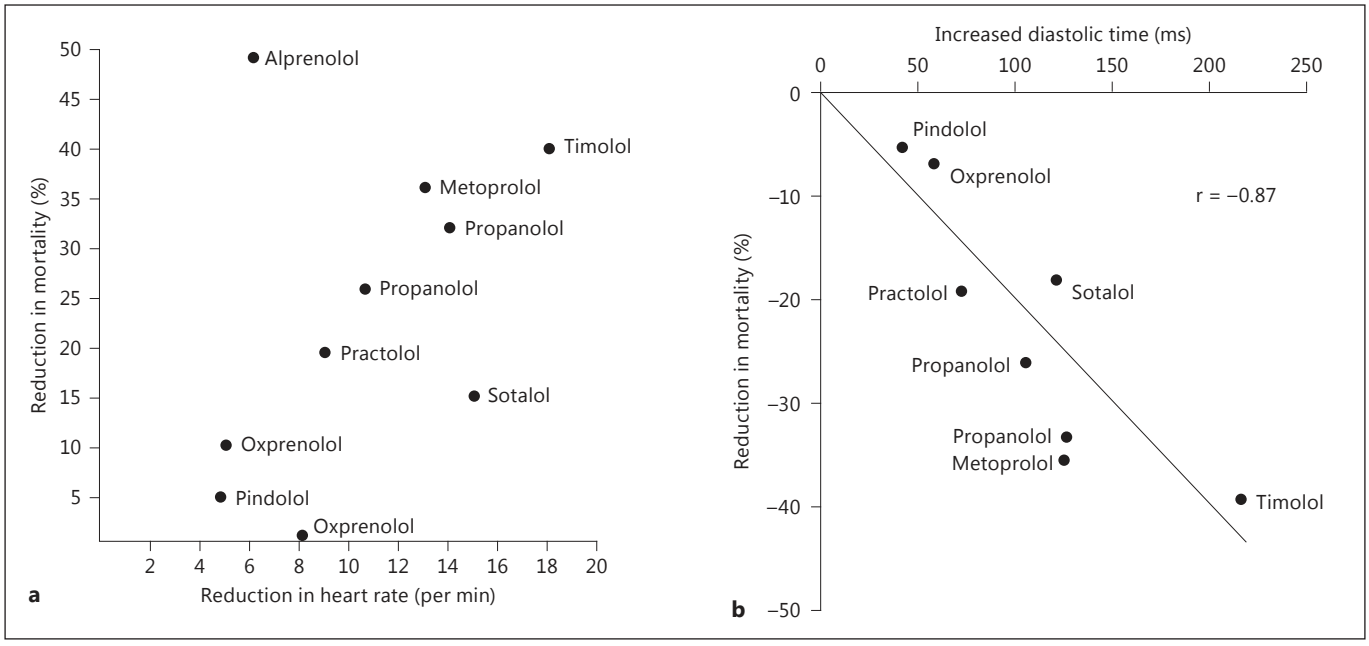

Fig. 8. a Relationship between reduction in heart rate due to therapy with β-blocking agents and reduction in mortality in large, prospective, randomized trials on patients with coronary artery disease [42]. **b** Relationship between increase in diastolic time due to therapy with β-blocking agents and reduction in mortality in patients with coronary artery disease in large, prospective, randomized trials [13].

supply of myocardial oxygen due to the increase in diastolic time at slower heart rates. An inverse relationship was present between diastolic time (in milliseconds) and mortality [12] (fig. 8b). In patients with silent myocardial ischemia, the number of ischemic episodes was substantially higher when the diastolic time decreased to <500 ms/beat (heart rate approximately 65–60 bpm) than when it was >500 ms/beat [10, 12, 44]. Support for the relationship of heart rate and coronary events has also been provided by experimental studies. Slower heart rates achieved with sinus node ablation in monkeys resulted in a decrease in the atherosclerotic process produced by a high-cholesterol diet when compared to monkeys whose heart rates were allowed to vary without sinus note ablation [45, 46].

β-Adrenergic blocking agents have other effects in addition to slowing heart rate. Some may be significantly beneficial, but some may be deleterious in certain patients. However, the relative importance of the effects of slowed heart rate on cardiac events can be inferred from studies with ivabradine, a drug that selectively inhibits the funny current (If), a small current that modifies the rate of the diastolic depolarization (pacemaker) current in the sinoatrial node, thereby selectively reducing the heart rate with no effect on myocardial contractility or arterial pressure [47]. In several trials, ivabradine decreased symptoms and myocardial ischemia in patients with stable angina pectoris. In the BEAUTIFUL study, ivabradine (n = 5,479) was compared to placebo (n = 5,438) in cardiovascular events in patients with stable coronary artery disease and LV systolic dysfunction. Background therapy included drugs commonly given to subjects with known coronary artery disease. The primary end point was a composite of cardiovascular death, hospitalized myocardial infarction and hospital admission with new onset or worsening heart failure. In this trial, ivabradine decreased heart rate, but failed to demonstrate primary composite end-point reduction for the entire study cohort. However, in a prespecified subgroup analysis in patients with a heart rate >70 bpm, ivabradine reduced nonfatal myocardial infarction at the 2-year follow-up [41, 48] (fig. 9a). Most recently, in the SIGNIFY (Study Assessing the Morbidity-Mortality Benefits of the If Inhibitor Ivabradine in Patients with Coronary Artery Disease) trial, the effect of ivabradine in patients with stable coronary artery disease without clinical heart failure and a heart rate ≥70 bpm were studied [49]. In addition to ivabradine, patients received therapy for stable coronary artery disease (antiplatelet therapy 97%, statins 92%, β-blockers 83%, angiotensin-converting enzyme inhibitors 27%, nitrates 40%,

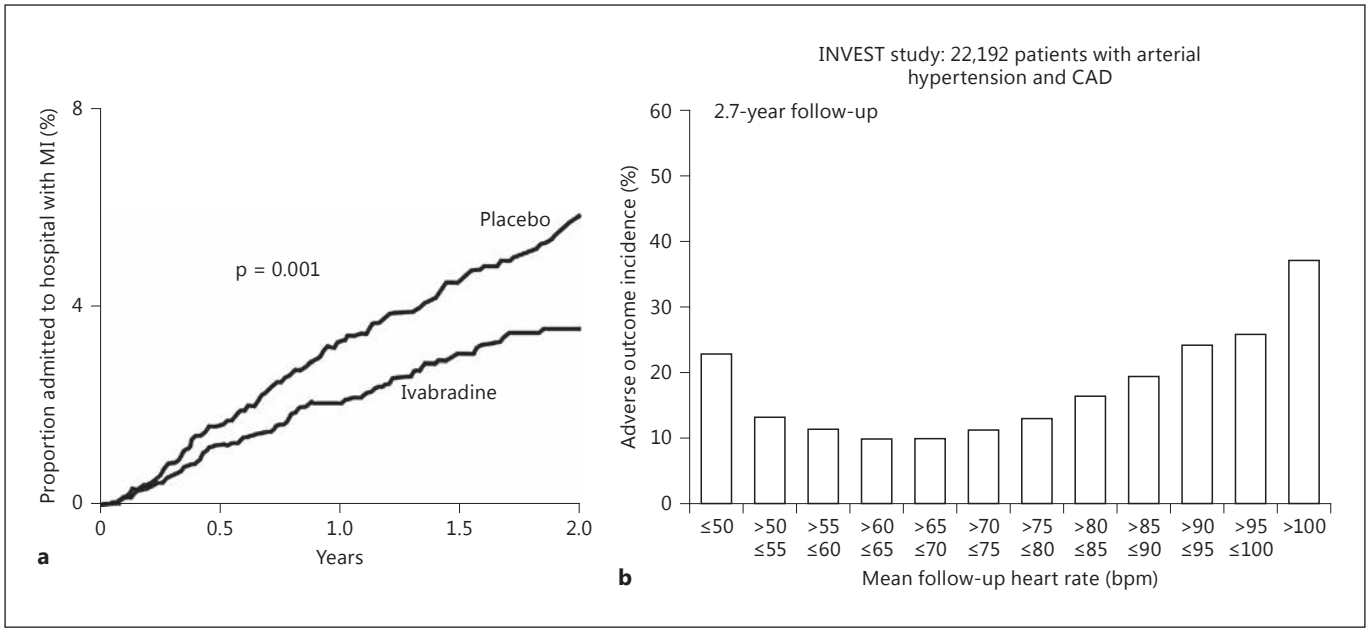

Fig. 9. a Proportion of patients with stable coronary artery disease and a heart rate >70 bpm at baseline who were hospitalized for myocardial infarction (MI). Therapy with ivabradine that decreased heart rate was associated with a decreased incidence of myocardial infarction [41]. **b** In patients with coronary artery disease (CAD) and arterial hypertension, the relationship between follow-up resting heart rate and the incidence of adverse outcomes is shown. Adverse outcomes include all-cause death, nonfatal myocardial infarction, or nonfatal stroke (modified from [53]).

diltiazem or verapamil 4.6%, and antidiabetic agents 40%). The primary end point (a composite of death from cardiovascular causes or nonfatal myocardial infarction) was not statistically significantly different between the 2 groups (ivabradine: n = 9,550, placebo: n = 9,552). However, among those who reported exertional angina when they entered the study, the incidence of the primary end point was higher in those taking ivabradine (7.6%) than in those on placebo (6.5%, p = 0.02). Ivabradine also increased the incidence of symptomatic bradycardia compared to placebo (7.9 vs. 1.2%), asymptomatic bradycardia (11 vs. 1.3%) and atrial fibrillation (5.3 vs. 3.8%). There are several plausible explanations for these findings. Ivabradine most likely had beneficial effects in some of the patients, but some of these were offset by the adverse effects of the drug (e.g. extreme bradycardia or atrial fibrillation). It should be noted that differences may exist between heart failure and coronary artery disease [50–52].

Patients with Coronary Artery Disease and Arterial Hypertension

In the INVEST (International Verapamil-SR/Trandolapril study) trial, 22,197 patients with a mean age of 65 years with stable coronary artery disease and arterial hypertension were randomized to either verapamil-SR or atenolol [53]. The primary end point was all-cause mortality, nonfatal myocardial infarction or nonfatal stroke; the average follow-up was 2.7 years. The study demonstrated that a relatively high baseline resting heart rate, or a relatively high or markedly slow resting heart rate during follow-up, was associated with adverse outcomes regardless of treatment strategy and underlying comorbidities (fig. 9b). Women had faster resting heart rates than men, while men for the same heart rates had a greater risk for adverse outcomes than women. The results have some similarity with the SIGNIFY trial, in which elderly patients with coronary artery disease in addition to state-of-the-art medical therapy also received ivabradine [49]. It should be emphasized, however, that antihypertensive agents have different effects on heart rate. A faster heart rate during therapy for hypertension may be associated with adverse events, regardless of the extent of changes in blood pressure. Thus, the so-called J-curve phenomenon in arterial hypertension may at least partially be related to an increase in heart rate and not only to changes in blood pressure [54].

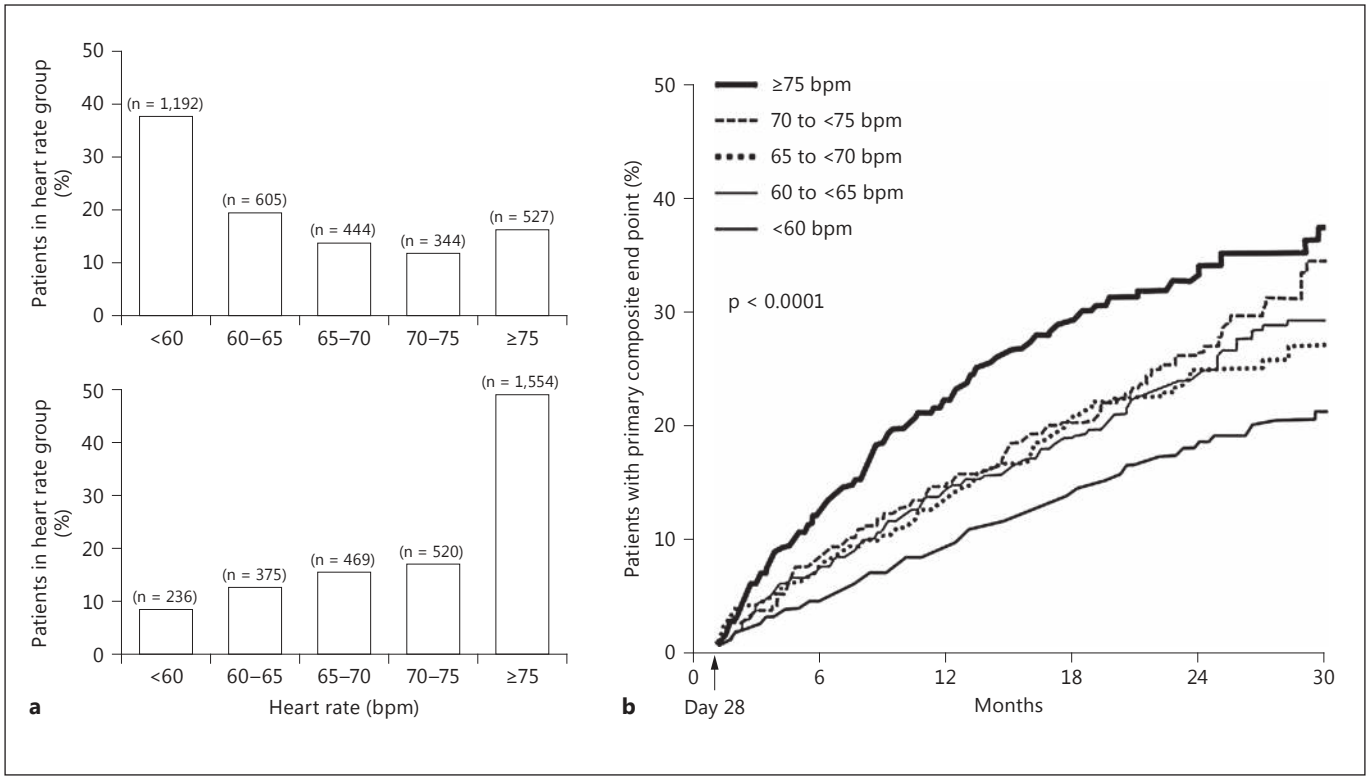

Fig. 10. a Distribution of patients in the ivabradine group (upper panel) and placebo group (lower panel) according to heart rate achieved at day 28. **b** Kaplan-Meier cumulative-event curves for primary end point (cardiovascular death or hospital admission for worsening heart failure) in the ivabradine group according to heart rate achieved at day 28 [63].

Patients with Heart Failure

Heart rate is an independent risk factor in patients with heart failure. Specifically in patients with heart failure and decreased systolic function, reducing heart rate improves outcomes, so heart rate reduction an important therapeutic target. β-Blockers are a first-line drug for the management of heart failure with decreased systolic function; they decrease heart rate and increase survival in patients with heart failure and decreased systolic function [55–60]. However, in addition to their effect on heart rate, β-blockers affect the cardiovascular system in other ways, perhaps not all beneficial [61–62]. In the SHIFT (Systemic Heart Failure Treatment with If Inhibitor Ivabradine) trial, which included patients with overt chronic heart failure and severe LV systolic dysfunction, 6,505 patients with LV ejection fraction (LVEF) ≤35% and a heart rate ≥70 bpm in sinus rhythm were evaluated in order to test the hypothesis that heart rate reduction with ivabradine, in addition to the background therapy suggested in the guidelines (i.e. 89% β-blockers, 91% renin-angiotensin system inhibitors and 60% mineralocorticoid receptor antagonists), can improve outcomes in patients with heart failure and decreased LV systolic function [63]. The addition of ivabradine (n = 3,241) reduced hospitalization or cardiovascular death compared to placebo (n = 3,364) during a median follow-up of 22.9 months (fig. 10). Within the range achieved, the lower the heart rate, the better the outcome; the best outcomes were observed among patients whose final therapy heart rate was 50–55 bpm. Therapy with ivabradine also resulted in a mild, but statistically significant increase in LVEF [63–67]. A slower heart rate results in decreased LV work, decreased myocardial demand for intracellular high-energy substrate (deficient in the myocytes of patients with heart failure and decreased LV systolic function) and increased myocardial blood flow, especially subendocardial blood flow, thereby enhancing the capacity to produce a high-energy substrate. These beneficial effects on myocardial energetics, arterial/aortic function and ventriculovascular coupling may partially explain the reported findings [7,10, 16].

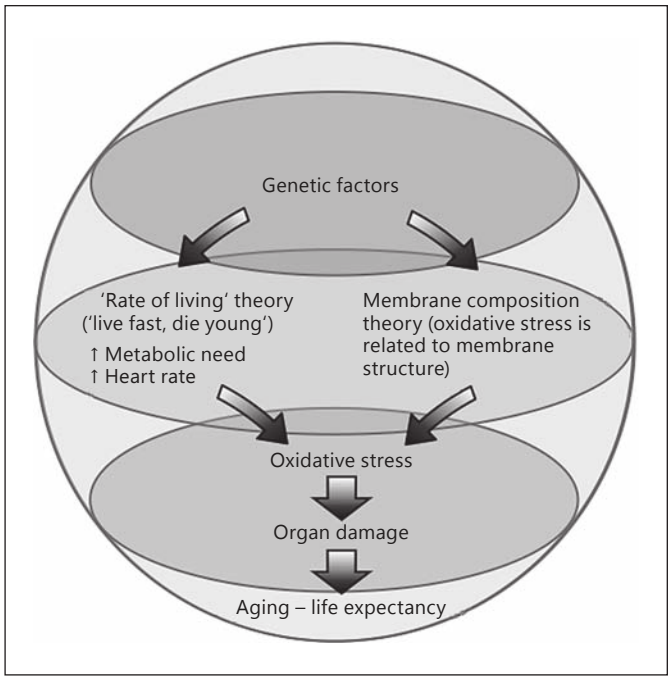

Fig. 11. Life expectancy is related to metabolic rate; an increase in metabolic rate leads to the production of free radicals and oxidative stress. Increased metabolic rate is also associated with a faster heart rate. Fatty acids that are involved in the structure of the cell membrane are also related to the degree of oxidative stress that leads to cell damage, aging and death. One theory is complementary to the other.

Heart Rate and Life Expectancy

Large animals have slower heart rates and live longer than small animals [1, 2]. An inverse relationship between heart rate and life expectancy has been found in mammals [1] (fig. 1). This observation was attributed to the higher metabolic rate in small versus large animals. A high metabolic rate leads to the development of free radicals, oxidative stress and faster aging. A high metabolic rate is associated with a faster heart rate, so the relationship between heart rate and life expectancy has been attributed to different metabolic rates in living organisms. This was originally described as 'the rate of living theory'.

As the size of an animal increases, although the animal requires more energy, the metabolic rate does not increase proportionally to the increase in body weight. Generally, in animals, and particularly in homeotherms, the rate of heat loss is a function of body surface area, while heat production is a function of body mass (weight). However, for a 2-fold (i.e. 100%) increase in body mass, body surface area only increases by approximately 59% [2]. This disproportional increase in body weight in relation to body area can also be seen in humans at different stages of development. In neonates (average weight: 3.5 kg, average body surface area: 0.25 m^2), the ratio of body weight to body area is 14 and at the age of 10 years (average weight: 30.5 kg, average body surface area: 1.14 m^2), this ratio is 27. In adults (average weight: 75 kg, average body surface area: 1.85 m^2), this ratio becomes 41. Thus, in large animals, the ratio of weight to body surface area is greater than in small animals, and the heat loss in relation to body weight is much less than in small animals. It follows that the metabolic rate per unit of mass in large animals is much smaller than in small animals.

Metabolic rate is a fundamental characteristic of all living organisms, and so life expectancy, to a certain degree, is related to metabolic rate. However, metabolic rate does not fully explain differences in life expectancy. Birds have a greater metabolic rate than mammals of similar size, but they live much longer. Metabolic rate also cannot explain the longer life expectancy of certain wild mice that live much longer than laboratory mice, certain types of rats that live up to 20–25 years (much longer than typical rats), humans, etc. [2].

More recent studies indicated that the oxidative stress that accelerates aging is also related to concentrations of lipids in the organism's cell membrane. A high concentration of polyunsaturated fatty acids in the cell membrane is associated with high oxidative stress and faster aging. In contrast, a low concentration of polyunsaturated fatty acids in the cell membrane is associated with lower oxidative stress and slower aging. Thus, the membrane composition theory may explain life expectancy in certain animal species in which the metabolic rate theory cannot. It appears therefore, that one theory may complement the other [2] (fig. 11).

Concluding Remarks and Therapeutic Considerations

ΜΗΔΕΝ ΑΓΑΝ (Nothing in Excess)
Temple of Apollo at Delphi

Heart rate is related to survival in apparently healthy individuals and in patients with different underlying cardiovascular diseases [1, 2, 68]. A decrease in heart rate due to therapeutic interventions may result in an increase in survival. The heart rate of individuals with sinus rhythm is regulated by the sinus node. Sinus node function is controlled by several mechanisms. Potassium and calcium

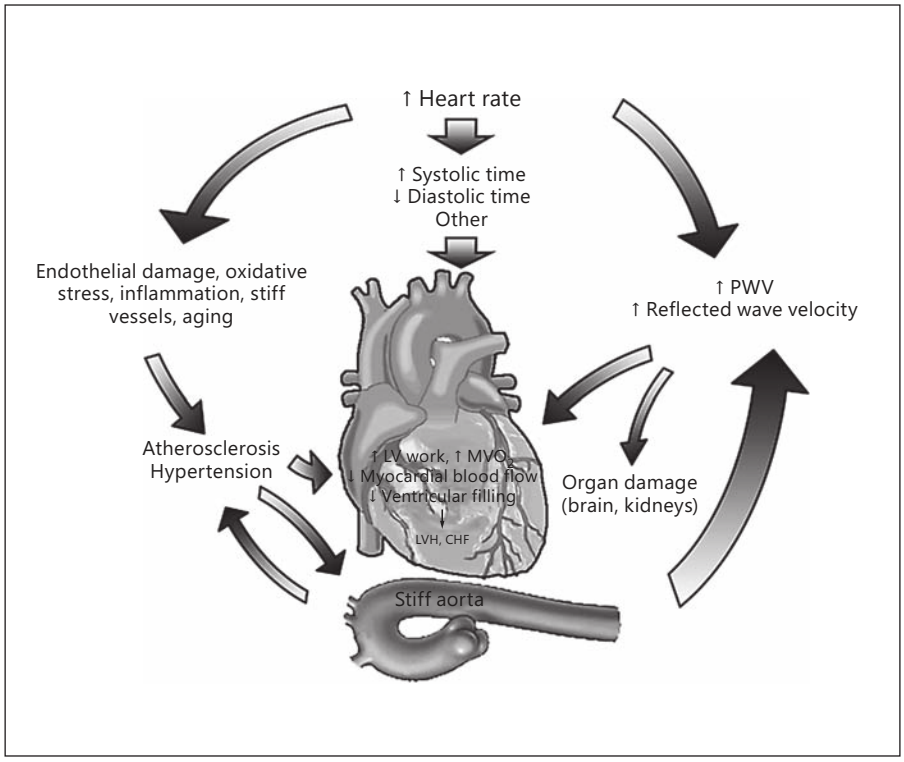

Fig. 12. Effects of heart rate on the cardiovascular system (schematic presentation). Increase in heart rate will result in a decrease in diastolic time and an increase in systolic time (increase in systolic time is proportionally less than the decrease in diastolic time); these changes result in decreased myocardial perfusion and increased LV work that in the long run, may result in LV hypertrophy (LVH), myocardial damage and congestive heart failure (CHF). Increased heart rate may also be associated with endothelial damage, oxidative stress, inflammation and stiff vessels, all of which may contribute to aging, the development of atherosclerosis, arterial hypertension and a stiff aorta. A stiff aorta results in an increase in pulse wave velocity (PWV) and reflected wave velocity that results in systolic hypertension, decreased myocardial blood flow and organ damage. All these effects of a fast heart rate on the cardiovascular system may contribute to the development of cardiovascular diseases and increase cardiovascular morbidity and mortality. MVO_2 = Myocardial oxygen consumption.

channels are the primary loci of the control of spontaneous diastolic depolarization and thus, of intrinsic heart rate in the sinoatrial node. Although If is quantitatively a relatively small current, it is a primary modulator of the slope of diastolic depolarization and thus, exerts an important influence over heart rate [3]. However, there are many other factors that directly or indirectly affect sinus node rate, such as autonomic nervous system activity, metabolic rate and inflammatory processes. Since many factors regulate heart rate, it may indeed be these factors, rather than the heart rate itself, that determine survival [4–6, 28–33]. However, heart rate has multiple direct effects on the cardiovascular system, regardless of the regulatory mechanisms. These effects directly affect the cardiovascular system in multiple ways that, in turn, may affect survival [7, 10, 11, 13, 16–20, 22, 23, 39, 69, 70] (fig. 12).

The effects of heart rate on LV work and MVO_2 have been well-appreciated for many years. More recently, the nonlinear relationship between heart rate and the diastolic time interval (i.e. the myocardial perfusion time) has been of increasing interest [7] (fig. 2). Thus, it became obvious that heart rate is not only an important factor in defining MVO_2 and high-energy substrate demand, but also for determining myocardial oxygen and high-energy substrate supply. For these reasons, slowing the heart rate has been a target for the management of patients with coronary artery disease. In the past, this goal was achieved with β-adrenergic blocking agents and, to a lesser degree, with verapamil-type calcium-channel blockers. These agents have several other effects on the cardiovascular system besides heart rate reduction. More recently, ivabradine, which selectively decreases heart rate without any other apparent effects on the cardiovascular system, has been introduced into clinical practice. Combinations of these drugs are often used [3, 41, 48, 49, 61, 70, 71]. Nonetheless, aggressive efforts to reduce heart rate among patients may produce substantial bradycardia, which without altering aortic function, may result in a substantial increase in central aortic pressure and the disappearance of the diastolic wave. This will result in an increase in LV work and MVO_2, and a simultaneous decrease in myocardial oxygen supply [16–19, 69] (fig. 4). These effects are opposite to what is expected from heart rate reduction. This may explain some of the negative results reported in patients with coronary artery disease who were treated with a combination of several bradycardic agents (β-blockers, calcium channel blockers or ivabradine).

Table 2. Fast heart rate: therapeutic considerations

- Apparently healthy individuals
  - Regular aerobic exercise 'ΜΗΔΕΝ ΑΓΑΝ' – 'nothing in excess'
  - Avoid stimulants (e.g. caffeine, alcohol, tobacco, other)
  - Maintain normal body weight
  - Close follow-up
- Patients with underlying disease
  - Management of the disease using current knowledge and common sense
  - Regular exercise when appropriate

Usually, when standard antianginal doses of β-adrenergic blocking agents are employed in patients with coronary artery disease, resting rate is maintained at <70 bpm. However, recent trials and registries indicate that among patients with heart failure and LVEF ≤35%, even when treated with β-blockers, resting heart rate exceeds 70 bpm in a substantial proportion of patients [68, 72–74]. In order to improve outcomes, these patients may need bradycardic drugs in addition to β-adrenergic blocking agents. Nonetheless, the addition of other bradycardic drugs to patients treated with β-blockers requires careful consideration from a physician who understands the physiology and pathophysiology of the coronary circulation, the effects of heart rate on the cardiovascular system, drug-drug interactions, and the medical problems of the individual patient for whom they are responsible. No clinical practice guidelines can fully address these issues [75].

At present, there is not enough information to justify treating individuals who have sinus tachycardia without evidence of underlying disease in order to slow the heart rate. It is reasonable, however, to instruct 'healthy' individuals with a fast heart rate to avoid stimulants such as caffeine, smoking, alcohol, etc. Regular aerobic exercise and maintenance of normal body weight also is suggested (table 2). In patients with an underlying disease and a fast heart rate, management using current knowledge, mild-to-moderate regular aerobic exercise, and common sense are important.

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