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Elevated Heart Rate: A Major Risk Factor for Cardiovascular Disease

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ABSTRACT

Mounting evidence shows that elevated heart rate is associated with a greater risk of developing hypertension and atherosclerosis and that it is a potent predictor of cardiovascular morbidity and mortality. These relationships have been shown not only in general populations but also among hypertensive individuals, with important implications for the treatment of hypertension. In spite of this evidence heart rate has been overlooked as a risk factor, but the fact that in most studies the risk related to fast heart rate remained highly significant after controlling for major risk factors for atherosclerosis suggests that it plays a direct role in the induction of the risk. The clustering of several risk factors for coronary artery disease in subjects with fast heart rate suggests that sympathetic overactivity accounts for the increased cardiovascular morbidity in subjects with tachycardia. In fact, experimental studies have shown that a heightened sympathetic tone can cause obesity, hyperinsulinemia, and insulin resistance which in the long run can promote the development of atherosclerosis. Moreover, experimental studies in the animal suggest that the heamodynamic disturbances related to high heart rate have a direct impact on the arterial wall promoting the development of atherosclerotic plaques. Preliminary results in the experimental animal and pooled data from intervention studies in patients with

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myocardial infarction or congestive heart failure suggest that drug-induced reduction of heart rate may be beneficial in several clinical conditions.

Key Words: Heart rate; Tachycardia; Hypertension; Insulin resistance; Sympathetic system; Cardiovascular risk.

INTRODUCTION

It is generally acknowledged that fast resting heart rate is associated with increased risk of cardiovascular morbidity and a large number of recent studies have led to a renewed interest in this clinical variable. However, accepted screening strategies for prevention of cardiovascular diseases do not include routine assessment of resting heart rate and most clinicians still do not think that reduction of fast heart rate should be pursued in otherwise healthy persons. Several large-scale trials have shown that heart rate-lowering treatment with beta-blockers significantly reduces cardiovascular events in subjects with myocardial infarction or heart failure. It is our opinion that fast heart rate should be decreased also in non cardiac subjects, although we readily admit that we have no definitive proof for such a statement. In the present review, we will briefly summarize the present knowledge on the relationship between heart rate and cardiovascular morbidity and will focus on some aspects which have hitherto not been fully elucidated.

THE EPIDEMIOLOGIC EVIDENCE

Attention on heart rate as a risk factor for atherosclerosis and cardiovascular events has been focused upon only in recent years. And yet, a highly significant association between resting heart rate and the incidence of myocardial infarction was demonstrated long ago in general population studies (1,2). It is noteworthy to observe that in the Glostrup study the predictive power of heart rate for coronary heart disease was even superior to that of cholesterol (1). The existence of a significant association between baseline heart rate and the likelihood of developing cardiovascular events in the subsequent years, independent of other major risk factors, was later confirmed by several leading epidemiologic studies (3–5). In the Framingham study (3) the predictive power of heart rate for all-cause mortality was equal to that of smoking and of systolic blood pressure, and in the Paris Prospective study (6) it was second only to smoking. In recent years, a mushrooming of new studies confirmed the strong association between high heart rate and cardiovascular disease clearly documenting that heart rate is a major risk factor for atherosclerosis and for cardiovascular and total mortality (7–9).

The results of several studies indicate that heart rate has an important clinical value also in the old age. In the Framingham (3) and the NHANES (5) studies the risk of mortality related to heart rate was spread all over the age range without any threshold level beyond which the risk was reduced. These results were confirmed by Aronow et al who found that the probability of developing new coronary events in elderly subjects was 1.14 times higher for an increment of 5 bpm of heart rate (10). In 763 men $\geq$65 years enrolled in the CASTEL study the relative risk for cardiovascular mortality

was 1.38 for the subjects of the top quintile of heart rate (>80 bpm) compared to those of the three intermediate quintiles (11). Conversely, men with heart rate < 60 bpm (bottom quintile) had a 0.82 lower risk of cardiovascular mortality than those in the three intermediate quintiles. In the Cox analysis the predictive power of heart rate for mortality in men was superior to that of the major risk factors for atherosclerosis. Two recent studies confirmed the strong association between fast heart rate and cardiovascular and all-cause mortality in the elderly. In the FINE study, Menotti et al showed that heart rate and smoking were the most important predictors of mortality in three male European populations (12). More recently, Palatini et al showed a similar association in the men and women with isolated systolic hypertension enrolled in the Syst-Eur study (13). In elderly subjects, tachycardia can be the marker of poor physical fitness and loss of vigor. In the CASTEL study the association of heart rate with cardiovascular mortality persisted after eliminating the subjects who died within the first two years after the baseline evaluation (11). Similar results were obtained in the FINE study when the subjects who died during the first five year of follow-up were discarded from the analysis (12) indicating that other mechanisms are responsible for the heart rate-death association.

In spite of this massive evidence, the importance of heart rate as a cardiovascular risk factor is still neglected by the scientific community, probably because the mechanism of the relationship between heart rate and mortality is poorly understood. In particular, heart rate is considered by most physicians a mere marker of risk rather than a true risk factor. In this review evidence will be provided that fast heart rate plays a direct role in the induction of the risk.

HIGH HEART RATE: RISK FACTOR OR RISK INDICATOR?

A close relationship between heart rate and blood pressure has been shown in several studies either in normotensive or hypertensive individuals (2–4,14). In four Chicago epidemiologic surveys correlation coefficients ranging from 0.2 and 0.3 were found (4). Similar correlation coefficients were found by other authors in both normotensive and hypertensive individuals (2,3,14). The relationship between heart rate and blood pressure held true in linear regression models, where age, gender, body mass index, smoking, alcohol intake, physical activity habits and other confounders were taken into account. Several other risk factors have been found to be related to elevated heart rate: hyperinsulinemia, increased blood glucose, high haematocrit, increased body mass index and lipid abnormalities (2,14). In the Tromso study, men with heart rate >89 bpm had 14.5% higher non-HDL cholesterol and 36.3% higher triglyceride levels than men with heart rate <60 bpm (15). In women the corresponding values were 12.5% and 22.2%, respectively. In both genders the heart rate-total cholesterol association was present in all categories of physical activity. Similar results were obtained in three general populations enrolled in the United States, in Belgium and in Italy (9). Subjects with tachycardia had high cholesterol and triglycerides, overweight and increased fasting insulin, showing the classical picture of the insulin resistance syndrome. The association of fast heart rate with high blood pressure, overweight, increased blood glucose and abnormal lipid profile has been found also in hypertensive cohorts (14).

The relation between tachycardia, hypertension and the metabolic abnormalities found in the above mentioned studies points to a role of sympathetic overactivity in determining the high heart rate and the metabolic disturbances (Table 1). The experimental evidence for the connection between increased sympathetic tone and the insulin resistance syndrome was provided by several groups of investigators who demonstrated that both acute and chronic stimulation of alpha and beta adrenoreceptors can lead to insulin resistance (2,14). Epinephrine infusion induces acute insulin resistance in healthy volunteers, and this can be blocked by propranolol. Chronic beta-receptor stimulation with epinephrine produces in animals a shift in skeletal muscle fibers, with an increase in rapidly contracting fibers, which is associated with insulin resistance. Vasoconstriction produced by alpha-adrenergic stimulation also induces insulin resistance, since it reduces the nutritional flow to skeletal muscle fibers and the glucose utilization (16). Another important reason for the linkage between high heart rate and cardiovascular mortality can be the decreased threshold for tachy-arrhythmias determined by the heightened sympathetic tone and the reduced vagal activity underlying tachycardia (2,14). The importance of this mechanism was documented by Lown and Verrier, who demonstrated that the threshold for arrhythmias in the dog was greatly decreased by an increase of sympathetic tone, and was increased by vagal stimulation (14).

According to the above pathophysiologic mechanism tachycardia might be merely considered an indicator of increased cardiovascular risk, as it reflects a heightened sympathetic activity. However, experimental evidence indicates that high heart rate is also an independent risk factor, and that it can promote the development of atherosclerotic lesions and favour cardiovascular morbidity and mortality through different mechanisms (Table 2). An elevated heart rate causes an increase in cardiac work (14). In fact, the energy expended by the heart is used mainly to achieve isovolumetric ventricular contraction. When the number of isovolumetric contractions per unit time increases, cardiac work will obviously become uneconomical. Tachycardia tends to intensify the pulsatile nature of arterial blood flow, and to produce oscillations in shear-stress direction, a phenomenon which in the long run is conducive to atherosclerosis (14). Mean blood pressure progressively increases with increasing values of heart rate up to the level of 140 bpm (14). This is due to the

Table 1. Tachycardia as marker of sympathetic overactivity.

Insulin resistance syndrome
Lower muscle capillary supply
Left ventricular hypertrophy
Small vessel hypertrophy
Decreased threshold for arrhythmias
Platelet activation
Increased hematocrit

Pathogenetic factors involved in the development of atherosclerosis and cardiovascular events.

Table 2. Tachycardia as independent factor in the induction of cardiovascular risk.

Increased cardiac work
Increased arterial wall stress
Higher mean blood pressure
Decreased large artery compliance
Disruption of vulnerable plaques
Increased ventricular vulnerability

increase in the total time spent on systole because of the shortening of diastolic time. Moreover, it has recently been demonstrated that a progressive increase in heart rate caused by pacing is accompanied by progressive and marked reduction in carotid artery compliance and distensibility (17). This might be due to the fact that it takes a certain time for the arterial wall to distend fully in response to blood pressure variations. The above mechanisms in the long run may cause endothelial damage thereby facilitating the development of wall lesions leading to atherosclerotic plaques. On the other hand, a direct action of heart rate in determining the atherosclerotic lesions was demonstrated by different groups of investigators in experimental studies (18,19). In cynomolgus monkeys in which heart rate was reduced either pharmacologically (18) or by ablation of the sino-atrial node (19) a retardation of the development of coronary lesions could be obtained.

Tachycardia has a pathogenetic role also in precipitating cardiovascular events in subjects at risk. Recent research has demonstrated that the hemodynamic stress related to high heart rate can favor the dysruption of a vulnerable coronary plaque (20). And it should be borne in mind that tachycardia can facilitate arrhythmias and precipitate sudden death also directly. An elevated heart rate may facilitate desynchronization of ventricular muscle cells, especially in an ischemic myocardium, increasing oxygen consumption and worsening coronary perfusion.

HEART RATE IN THE ANIMAL KINGDOM

It is common knowledge that heart rate is highly variable throughout mammals with high values in small animals and lower values in larger ones (21). The main reason for these differences seems to be the different metabolic rate in the animals. Small homeotherms necessitate an increased metabolic rate to prevent a fall in body temperature, which seems to be responsible for the fast heart rate. In mammals, there is a linear inverse logarithmic relation between heart rate and body mass and a linear inverse semilogarithmic relation between heart rate and life expectancy (21). If one accepts the notion that there is an inverse relation between heart rate and life expectancy, then each species should have a predetermined number of heart beats in a lifetime. As a matter of fact, if in mammals the number of heart beats in lifetime is plotted against life expectancy, it can be seen that the total number of beats is fairly constant and that all species lye on a vertical line. This indicates that life span is predetermined by basic energetics of living cells and that heart rate is a main

determinant of life expectancy. Whether factors which accelerate average heart rate can shorten life expectancy, and those which reduce heart rate can extend life is a fascinating but still unanswered question.

THERAPEUTIC PERSPECTIVES IN HYPERTENSION

The syndrome of hypertension is a complex one, including a constellation of metabolic and haemodynamic abnormalities which are independently conducive to coronary atherosclerosis and to cardiovascular events. This suggests that in the treatment of hypertension optimal results could be obtained with agents that besides lowering blood pressure also reduce other negative effects of increased sympathetic tone, in particular increased heart rate. A beneficial effect of heart rate reduction was demonstrated with the use of beta-blockers in monkeys, in which a retardation of the development of atherosclerotic lesions was achieved (18). Moreover, heart rate reduction with digoxin proved to be efficacious in prolonging life in mice (22).

A beneficial effect of heart rate reduction has been shown also in human studies. Several trials have shown that beta-blockers are useful in reducing mortality rate in post-myocardial infarction subjects and in patients with congestive heart failure and that the advantage of treatment is proportional to the reduction in heart rate achieved (22,23). The results of beta-blockers therapy in human hypertension were less impressive, probably due to the impairment in the metabolic profile often observed with these drugs. Propranolol was shown to reduce HDL-cholesterol and to decrease insulin sensitivity by 32%, an effect which was less evident but still present with the cardioselective beta-blocker metoprolol (−15%), or with pindolol (−17%) (22). Several clinical trials have shown that hypertensive subjects on beta-blockers tend to gain weight over time in comparison with patients taking other antihypertensive drugs (22). Thus, the metabolic effects of beta-blockers may limit their efficacy at least in the insulin-resistant and dyslipidemic proportion of the hypertensive population.

A better effect in the treatment of hypertension should be achieved with drugs that reduce heart rate and sympathetic activity without impairing the metabolic profile. Several classes of antihypertensive drugs seem to possess these properties. Moxonidine, rilmenidine and clonidine through their action on the imidazoline-1 receptors proved to be efficacious in inhibiting the discharge of the vasomotor neurons located in the rostral ventrolateral medulla (22). Moxonidine actually showed a favourable metabolic profile in human studies, and reduced plasma renin and catecholamine levels (22).

Phenylalkylamines also have a number of specific properties that influence sympathetic outflow. The observation that verapamil penetrates the blood-brain barrier and is found in cerebrospinal fluid suggests that it might be capable of central actions that limit sympathetic outflow (22). It has been recently demonstrated that chronic verapamil administration caused a significant reduction in epinephrine, norepinephrine, dopamine and chromogranin A, along with a significant decline in heart rate and blood pressure response to α-blockade (22). Although the superiority of antihypertensive drugs which reduce heart rate and sympathetic activity has not been demonstrated in clinical trials, these agents have a good potential for reducing cardiovascular morbidity and mortality in hypertensive patients, at least in those individuals with hyperdynamic circulation and the features of the insulin resistance syndrome.

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