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Perspectives of I_f Inhibition by Ivabradine in Cardiology

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Abstract

High heart rates predict cardiovascular morbidity and mortality in the healthy population, in hypertensive patients, and in those with coronary heart disease (CHD) or heart failure. I_f channel inhibition with ivabradine is an effective approach to reduce heart rate pharmacologically, with the prospect of preventing complications. The antianginal effects of heart rate-lowering with ivabradine have been shown to be similar to those with β-adrenoceptor antagonists (β-blockers) in patients with CHD. The BEAUTIfUL and SHIfT trials will provide evidence on whether I_f channel inhibition with ivabradine is able to reduce mortality and morbidity in patients with CHD with impaired left ventricular function and heart failure.

Future perspectives for additional study are potential roles of ivabradine in the treatment of hypertension and atherosclerosis, and their complications. Further clinical and mechanistic studies to clarify the pathophysiological background are needed to fully define the role of heart rate reduction in the broad spectrum of cardiovascular interventions.

1. Heart Rate in Cardiovascular Pathophysiology

Both heart rate and stroke volume are the main factors for effectively adapting cardiac output to metabolic demands of the organism. Heart rate itself is highly variable and therefore predominantly acts as the driving force for cardiovascular regulation in mammals, including humans. Heart rate closely contributes to myocardial work and energy requirements, thus influencing the balance of cardiac performance and economy. Because of myocardial mechanical and metabolic stimulation, it seems plausible that heart rate can impose stress not only on the myocardium but also on the peripheral vasculature, and may therefore play an important role in determining cardiac and vascular end-organ damage, thereby exhibiting a strong influence on life expectancy.[1] The understanding of the fundamental effects of heart rate on morbidity and mortality in the general population and in different cardiovascular disease states has provided the rationale for pharmacologically reducing heart rate with the recently developed concept of I_f channel inhibition with ivabradine.

2. Heart Rate and Survival in the General Population

Experimentally, the pharmacological reduction of heart rate by cardiac glycosides such as digitalis caused a 30% prolongation of survival time in healthy mice (figure 1).[2] This, and the previously mentioned energy considerations concerning high

heart rates, may possibly support the notion that reduction of heart rate itself prolongs survival time in mammals, at least in part independently of the activity of the autonomic nervous system. The correlation of heart rate and life expectancy, as demonstrated in mammals, also holds true for the human population. Epidemiological studies investigating approximately 30 000 individuals over a period of 5–36 years clearly revealed an inverse relationship between heart rate and survival time in the general population (figure 2).[3-8] According to the CASTEL (CArdiovascular STudy in the ELderly) trial, this relationship is especially true for patients older than 65 years.[9] Furthermore, the maximal heart rate developed during exercise, the difference between resting heart rate and maximal heart rate during exercise, and the time course of the heart rate returning to normal values after exercise are risk factors of sudden cardiac death.[10,11] When heart rate at rest is about 88–99 beats/min compared with heart rates of 60–65 beats/min,[4,5] there is a 5- to 6-fold increase of risk for sudden cardiac death in men and a 2-fold increase in women. The total mortality rate doubles with a rise in heart rate of about 40 beats/min.[12,13] These correlations can be strengthened when additional risk factors such as age, hypertension, diabetes mellitus and high body mass index are present. The recent European Society of Cardiology 2007 guidelines recommend heart rate reduction by

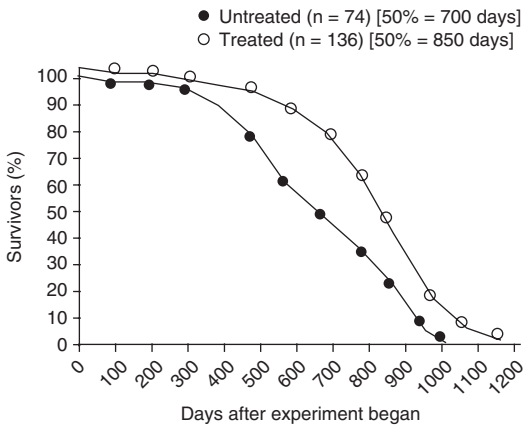

Fig. 1. Comparison of survival time in healthy mice and in mice treated with a digitalis dosage that produced a 30% reduction in heart rate (modified from Coburn et al.[2]).

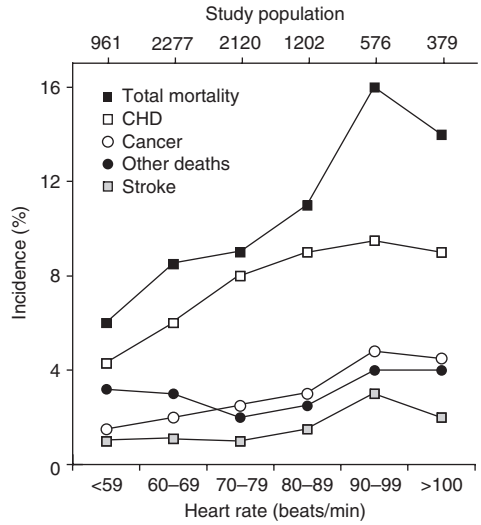

Fig. 2. Relationship between the heart rate and the incidence of total mortality, coronary heart disease (CHD), cancer, other deaths and stroke (adapted from Wilhelmsen et al.[6]).

exercise and other non-pharmacological methods in healthy populations, but pharmacological heart rate reduction, although an attractive option, is not yet recommended.[14]

3. Arterial Hypertension

The association between heart rate and the development of arterial hypertension was first demonstrated in a 1945 analysis of soldiers following their service in World War I.[15] These findings were supported by the prospectively designed HARVEST (Hypertension and Ambulatory Recording Venetia Study),[16] which revealed a strong link between higher heart rates and increases in blood pressure in a cohort of stage 1 hypertensive patients. Patients of this cohort whose heart rate was persistently elevated during the study period of 6.4 years had a doubled fully adjusted risk of developing fixed hypertension compared with individuals with normal heart rates. This correlation was modified by risk factors such as age, body mass index, smoking, alcohol consumption and physical inactivity. Furthermore, the rate of complications caused by cardiovascular disease, as well as the total mortality

in patients with hypertension, increases by about 100% when heart rate increases by 40 beats/min.[17]

4. Atherosclerosis

The stiffness of arterial vessel wall worsens with increasing heart rates. This correlation is particularly found in patients with hypertension. The combination of increased blood pressure with repetitive pressure changes caused by higher heart rates imposes an additional mechanical load on the vessel wall which is consequently more prone to enlargement of damage.[18] Haemodynamic stress induces endothelial dysfunction. Mangioni et al.[19] demonstrated that tachycardiac pacemaker stimulation increased the stiffness of carotid arteries. Monkeys showed a strong correlation between an increased haemodynamic stress index (heart rate times mean arterial blood pressure) and the development of atherosclerosis in the aorta or iliac vessels.[20] Furthermore, heart rate reduction caused by sinus node ablation was associated with a decrease in coronary atherosclerotic lesions in monkeys fed a cholesterol-rich diet.[21] Additionally, in young patients with myocardial infarction there is a strong positive relationship between higher heart rates and the extent of atherosclerotic coronary lesions.[22]

Taken together, an elevated heart rate has adverse effects on the development of cardiovascular endpoints, resulting in morbidity and mortality in the general population and in patients with cardiovascular disorders with an *a priori* low risk such as hypertension or atherosclerosis. The mechanisms of the deleterious effects of high heart rate have been identified as an acceleration of atherosclerosis, the production of plaque instability, as well as the facilitation of occurrence of sudden cardiac death. Therefore, I_f channel inhibition with ivabradine has been identified as having a great potential to reduce heart rate and presumably decrease the number of adverse cardiovascular events. However, the identification of patients at particularly high risk and prospective controlled clinical trials are needed to prove this concept in diseases with an *a priori* low risk. In addition, pathophysiological mechanisms have to be identified before I_f channel inhibition can be included as part of the standard treatment of these conditions.

5. Coronary Heart Disease and Myocardial Infarction

The long-term prognosis of patients with stable coronary heart disease (CHD) is correlated with resting heart rate.[22,23] Several trials have demonstrated the relevance of heart rate for the prognosis of patients after myocardial infarction. According to Hjalmarson et al.,[24] the heart rate of patients with myocardial infarction was significantly higher than that of the control group. Furthermore, higher heart rates of these patients at hospital discharge correlated with an increase in mortality rate after 1 year. Meta-analyses of the GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico)-2 and GISSI-3 trials, including about 20 000 patients, demonstrated that the inhospital mortality rate of patients after myocardial infarction rose from 3.3% to 10.1% when patients with heart rates <60 beats/min were compared with those with heart rates >100 beats/min on admission, even in patients without heart failure.[25] Finally, heart rate reduction is correlated with an improvement in long-term survival of patients with myocardial infarction, best demonstrated in the β-adrenoceptor antagonist (β-blocker) trials (figure 3).[26]

The development programme for I_f channel inhibition by ivabradine has been well advanced in the field of CHD. Clinical studies have shown that there are pronounced anti-ischaemic and antianginal actions in patients with stable angina pectoris.[27] The effect has been shown to be similar to the antianginal and anti-ischaemic effects of β-blockade.[28] Experimental studies have shown that there is a clear reduction of ischaemia and also a reduction of post-ischaemic remodelling with ivabradine.[28] The great relevance of I_f channel inhibition by ivabradine in CHD is shown by the high number of patients in whom treatment does not completely abolish ischaemia or does not adequately control symptoms of ischaemia. There are several groups of patients in whom revascularisation is not possible as a result of diffuse coronary artery atherosclerosis,

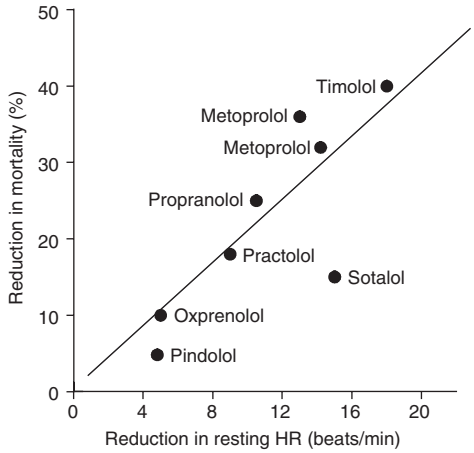

Fig. 3. Relationship between reduction in mortality and reduction in resting heart rate with β-adrenoceptor antagonists (β-blockers) in patients with myocardial infarction (adapted from Kjekshus and Gullestad[26]).

previously performed coronary artery bypass graft surgery or percutaneous interventions without technically achievable complete revascularisation, lack of graft material, severe co-morbidity preventing interventions or operations, as well as advanced age. In those patients, the unmet need for other antianginal therapy options is clearly evident. In ARTS (Arterial Revascularization Therapies Study),[29] even after revascularisation, a significant number of patients had to be maintained on antianginal medication. The percentage of patients who remained free of antianginal medications following percutaneous transluminal coronary angioplasty was 16.4% after 1 month, 18.6% after 6 months and 21% after 12 months.[29] In patients who underwent cardiac surgery, the numbers who remained free of antianginal medications were higher, but still <50% (1 month 29.4%, 6 months 39%, 12 months 41.4%).[29] In addition, in the Euro Heart Survey,[30] it was clearly shown that the revascularisation frequency in European patients is quite low, and that the majority of patients have to be treated with antianginal drugs (figure 4).[30]

Classical antianginal treatment with β-blockers might be limited, because of potential contraindications or adverse drug effects such as bradycardia, atrioventricular conduction disturbances, negative inotropy, blood pressure-lowering effects, bronchial spasm in asthma, or metabolic effects. Other drugs can produce intolerance or headache (nitrates), or produce peripheral oedema or reflex tachycardia (calcium channel antagonists). Therefore, there is an unmet need for antianginal interventions. I_f channel blockade with ivabradine has no effect on myocardial contractility or intracardiac conduction, has a lack of rebound phenomena, has no effect on tolerance, and lacks effects on metabolic parameters or haemodynamics.[31] Therefore, the potential of this concept could be particularly successful in patients with bronchial asthma, peripheral arterial disease, atrioventricular conduction delay, hypotension and psoriasis, as well as in some patients with diabetes mellitus and patients developing erectile dysfunction with a β-blocker.

Beyond reduction of stable angina pectoris, heart rate reduction might also provide prognostic benefits. The rationale for this is:

- mortality and morbidity remain high in patients with CHD;[23]
- resting heart rate has an independent prognostic value in CHD;[23]
- relationship between heart rate reduction and decrease in mortality in patients with myocardial infarction and heart failure has been shown with β-blockers;[24]
- significant numbers of patients are not prescribed β-blockers;[24]

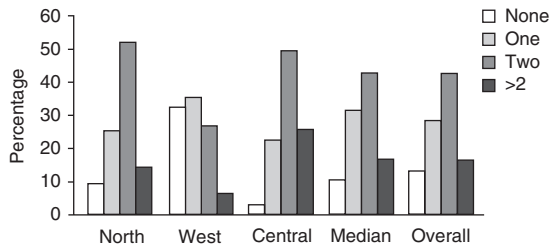

Fig. 4. Consumption of antianginal medication by patients with stable angina pectoris in European countries according to the Euro Heart Survey.[30] It is interesting to note that on average, 13% of patients in central Europe with coronary heart disease were not treated with an antianginal drug. The majority of patients received one or more drugs, even though some patients had undergone revascularisation procedures (adapted from Daly et al.[30]).

- unique pharmacodynamic profile of ivabradine to control heart, with lack of any deleterious impact on haemodynamics in unstable patients;[31]
- beneficial effects of ivabradine on cardiac remodelling, capillary density and left ventricular dysfunction in models for cardiovascular disease.[28]

6. Heart Failure

Neuroendocrine mechanisms, such as increases of sympathetic activity and activity of the renin-angiotensin-aldosterone system, are activated in heart failure and contribute to a progression of ventricular dysfunction. High heart rates are negative prognostic predictors in patients with heart failure.[32] Furthermore, high heart rates *per se* can cause heart failure. As known from patients with atrial fibrillation and an inadequate heart rate control, a decline in ventricular ejection fraction can occur within days.[32] After control of ventricular rate, gradual improvement of left ventricular function can be achieved in the following weeks and months.

The normal heart develops a stepwise rise in contractility when heart rate is accelerated. This positive force-frequency relationship (Treppe [staircase] phenomenon or Bowditch-effect)[33] is abolished or inverted in the failing myocardium. The heart rate-associated impairment of relaxation is especially important in hearts with diastolic heart failure.[34,35] Diastolic heart failure is characterised by an impaired relaxation and/or decreased compliance of the ventricle while systolic function is largely preserved. The heart rate-related decline of relaxation additively compromises the pre-existing relaxation disturbance of these hearts. This view is in concert with the results of heart failure trials.[26,36] All treatment strategies resulting in heart rate reduction improved prognosis, while those accompanied by an increase in heart rate exhibited adverse effects on survival.

Even in the presence of full neuroendocrine antagonism including β-blockers, the heart rate can be high in a considerable number of patients.[26] In particular, even in the presence of the β-blocker, the outcome of heart failure is still related to heart rate.[26] Recent reports show beneficial effects of ivabradine in heart failure even in patients receiving β-blockers.[36,37] This is the rationale for I_f channel inhibition by ivabradine in chronic heart failure. The BEAUTIfUL (morBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction) study is investigating patients with impaired left ventricular function and CHD.[37] The primary endpoint is a composite of cardiovascular mortality and hospital admission for acute myocardial infarction or new

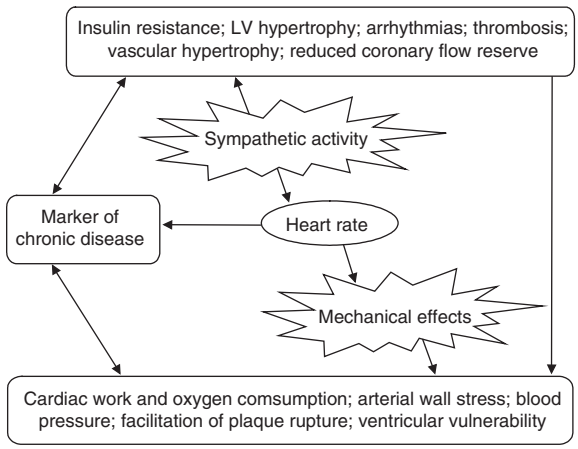

Fig. 5. Central role of heart rate in producing end-organ damage, and its relation to neuroendocrine activation and direct mechanical effects. **LV** = left ventricular.

onset or worsening of heart failure. This event-driven study will randomise 9650 patients and will be the first major outcome trial with a specific heart rate-reducing agent in CHD.[37] SHIfT (Systolic Heart failure treatment with the If inhibitor ivabradine Trial) will investigate patients with reduced left ventricular function because of various causes.[38] The study has started to recruit patients and will be the largest trial to examine the clinical outcome of I_f channel inhibition with ivabradine. These major outcome trials will provide definite evidence whether or not heart rate reduction on top of standard medication for chronic heart failure will be able to improve morbidity and mortality.

7. Conclusions

Evidence has been provided that an increase in heart rate is relevant for morbidity and mortality in individuals from the general population and in patients with cardiac disease with low event rates, and also in those with symptomatic CHD, myocardial infarction or with chronic heart failure.[39,40] Outcome studies and the development programme for ivabradine to inhibit I_f channels, in particular the studies on CHD as well as heart failure (BEAUTIfUL, SHIfT), will provide definite evidence for a potential beneficial effect of selective heart rate reduction in chronic heart failure. High resting heart rate has a strong relationship with the sympathetic nervous system activity, and also produces a direct mechanical effect on myocardial work and oxygen consumption, vascular wall stress and blood pressure, and can produce plaque rupture or ventricular arrhythmias (figure 5). Even in the absence of chronic disease, where it can be a marker of disease, there are direct effects on the cardiovascular system which set the stage for addressing CHD and heart failure by I_f channel inhibition with ivabradine to reduce cardiovascular morbidity and mortality. Further mechanistic and clinical study will be needed to determine its potential role in hypertension and atherosclerosis to prevent the development of cardiovascular complications.

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