Heart rate management: a therapeutic goal throughout the cardiovascular continuum

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A number of physiological pathways and risk factors leading to cardiovascular disease (CVD) are now well identified, although there are still aspects to be investigated. An interesting concept has been developed called the CVD continuum which frames CVD as a chain of events initiated by a number of risk factors leading to end stage of the disease with the hypothesis that any interruption along this chain of events may interrupt the pathological process thereby conferring cardiovascular prevention. In recent years, heart rate (HR), a simple and familiar clinical finding, has been shown to be an independent risk factor of mortality and morbidity in various populations including patients with CVD. This review shows that high HRs intervene along the chain of events which constitutes the cardiovascular continuum promoting CVD. Experimental data and clinical observations that demonstrate the major role played by resting HR in the pathophysiology of atherosclerosis through the stress exerted on the vascular endothelium leading to atherosclerotic lesion formation and plaque rupture are reviewed. Therefore, HR reduction should lead to prevention of atherosclerosis and therefore to the reduction of cardiovascular events. Trials have been undertaken to answer this question and the results are expected in the near future.

KEYWORDS
Heart rate; Risk factors; Cardiovascular disease continuum; Coronary artery disease

Introduction

Cardiovascular disease (CVD) is common in the general population and represents an important public health problem. A number of physiological pathways leading to CVD have been identified, although there are still a number of processes which remain to be clarified. Dzau et al.1 came out in 1991 with a concept called the CVD continuum which framed CVD as a chain of events initiated by a number of risk factors leading to end stage of the disease and hypothesized that any interruption along this chain of events may interrupt the pathological process thus conferring cardiovascular prevention.2 In recent years, heart rate (HR), a simple and familiar clinical finding, has been shown to be an independent risk factor of mortality and morbidity in various populations including CVD.3–6

The aim of this paper is to show how high HR may intervene to promote CVD along the chain of events which constitute the cardiovascular continuum.

The cardiovascular disease continuum

Epidemiological studies have identified well-known risk factors such as dyslipidaemia, arterial hypertension, diabetes mellitus, smoking, and obesity, mainly visceral adiposity as part of the so-called metabolic syndrome.7,8 These risk factors may promote atherosclerosis and/or left ventricular (LV) hypertrophy. The most common and life-threatening manifestation of atherosclerosis is coronary artery disease which has two major clinical presentations, i.e. stable angina pectoris related to myocardial ischaemia and acute myocardial infarction. Among the possible complications of myocardial infarction, ventricular arrhythmias with the risk of sudden cardiac death and loss in myocardial tissue inducing ventricular remodelling and ventricular...
enlargement leading to heart failure and end-stage heart disease are life-threatening (Figure 1). This review article aims to demonstrate how HR may intervene in the cascade of events that constitute the CVD continuum.

Heart rate and cardiovascular mortality

Many clinical or epidemiological studies have shown that resting HR is an independent risk factor of total mortality and cardiovascular mortality. These studies have been analysed by Aboyans et al. and others. Overall, they include 15,500 patients followed up for 8–36 years. For example, the ‘Chicago Peoples Gas Company study’ included 1,223 men followed up for 15 years. Two other cohorts of patients belong to the ‘Chicago Western Electric Company’ and to the ‘Chicago Heart Association Detection Project’ included 1,899 and 5,784 men followed up for 17 and 5 years, respectively. A relation was found between HR and cardiovascular mortality and total mortality. Similarly, the Framingham study showed with a 30-year follow-up that a significant relationship exists in men as in women, between high resting HR and the increase in cardiovascular mortality, coronary heart disease, and sudden coronary death. The MATISS Project included 2,533 men aged 40–69 followed up for a total of 24,457 subjects-years and showed that HR was an independent predictive factor for total mortality, cardiovascular mortality and non-cardiovascular mortality. Jouven et al. reported a French population of 5,713 asymptomatic working men (between the ages of 42 and 53 years) with a 23-year follow-up and found that after adjustment for potential confounding variables resting HR was significantly associated with an increase in sudden death and non-sudden death from myocardial infarction. Wide variations of HR were analysed in these studies. Some compared HR of <60 bpm with HR above 90 or even 100 bpm Jouven et al. compared those subjects with a resting HR above 75 bpm with those with a HR below 60 bpm and found that those with high HR had a relative risk of sudden death from a myocardial infarction of 3.92 (95% CI).

The question of the optimal HR often arises and faces the difficulty of the wide variation seen over a 24-h period with a circadian rhythm, the fact that HR decreases with age, that HR is generally higher in women than in men, and that it varies with the position (sitting vs. supine) in which it is measured. Palatini et al. recommend in a consensus that HR should be measured by pulse palpation over two periods of 30 s each after 5 min in a quiet room in a sitting position.

Cardiovascular disease and the pathophysiological continuum

The pathophysiological processes known to initiate CVD include oxidative stress, endothelial dysfunction, inflammation, and vascular remodelling (Figure 1). Knowledge gained in the understanding of these processes has promoted the development of new therapeutic strategies. These processes may lead to tissue damage characterizing atherosclerotic disease. Oxidative stress results in reduction in nitric oxide (NO) activity and endothelial dysfunction. The latter induces pathological vascular responses, e.g. vasoconstriction, inflammation, muscle cell proliferation, and thrombosis. The renin–angiotensin–aldosterone system plays an important role in the CVD continuum. Inhibition of angiotensin-converting enzyme and angiotensin II through the AT1 receptors is used in the management of CVD, particularly the treatment of hypertension and of congestive heart failure (CHF). Other hormones such as atrial natriuretic peptide and brain natriuretic peptide, endothelin, pros-tacyclin, and prostaglandin E are also involved in the pathophysiology of CVD. Inflammation is associated with endothelial injury and with the development of atherosclerosis to the point that C-reactive protein has become a marker of CVD risk. Vascular remodelling represents the structural transformation resulting from changes of haemodynamic conditions as seen in arterial hypertension. It is important to underline that several processes are taking place simultaneously to generate CVD.

Experimental evidence of the role of heart rate in the cardiovascular continuum

In order to understand the role of HR in endothelial dysfunction and atherosclerotic lesions, basic knowledge of local haemodynamic forces imposed on the arterial wall is necessary. These forces include flow-generated shear stress which is the tangential forces due to the friction of the blood flowing on the endocardial surface and blood-pressure-derived tensile stress, also called circumferential stress, which represent the blood-pressure-derived force imposed on the circumference of the arterial wall. Low shear stress stimulates mechanoreceptors located on the surface of endothelial stress transducing them into biochemical signals (mechanotransduction) which cannot be developed in detail here but which are well explained in the excellent review of Giannoglou et al. Tensile stress is also sensed by mechanoreceptors which trigger a cascade of signalling molecules. Elevated tensile stress is thought to induce direct endothelial injury and to increase endothelial permeability to LDL.
and to circulating inflammatory mediators. Very high HR (>120 bpm) by reducing the diastolic phase reduces the stroke volume and the cardiac output. Moderate tachycardia (close to 100 bpm) increases blood pressure and the tensile stress and may promote endothelial injury and wall stiffness.

The role of HR in myocardial ischaemia as seen in patients with stable angina and those who suffered a myocardial infarction is also well established (Figure 2). It is well known that increased HR is present in angina pectoris and myocardial ischaemia as a consequence of exercise or emotional stress. Several mechanisms may account for the increase in HR including catecholamine discharge. Kop et al.15 analysed HR variability (HRV) 1 h before and after ischaemic events in 19 patients who underwent 24 h ambulatory recordings and assessed the role of exercise and mental stress on pre-ischaemic autonomic changes. Ischaemic events at high mental stress were preceded by depressed high frequency HRV levels compared with events at low mental activity, whereas the effects of mental activities were not observed during non-ischaemic control periods.

HR may be involved at different phases of the development of atherosclerosis, in plaque erosion, and plaque rupture resulting in thrombosis and in acute coronary event (Figure 3).

Experimental evidence supports the role of HR reduction in the progression of atherosclerosis. Beere et al.16 investigated the role of HR reduction in six monkeys (Macaca fascicularis) fed with an atherogenic high cholesterol diet for 6 months. These animals underwent sinus node ablation and compared with eight animals which had the same operation without sinus node ablation. Coronary atherosclerosis was less than half in the group with low HR related to sino-atrial ablation when compared with the control group without sino-atrial ablation suggesting a protective effect of lower HR. Yamamoto et al.17 in an isolated sino-atrial preparation in hypertensive rats showed that the increase in HR with cardiac pacing, therefore independent of sympathetic nerve activity, enhances cardiac oxidative stress and activates mitogen-activated protein kinases, which seem implicated in cardiac hypertrophy and cardiac remodelling. Guth et al.18 evaluated the beneficial effect of intravenous atenolol on exercise-induced regional myocardial ischaemia and contractile dysfunction in conscious dogs with single-vessel coronary stenosis. The regional dysfunction was reduced with atenolol but the improvement is prevented if HR is kept constant with atrial pacing. Therefore, HR reduction may play an important role in the CVD continuum.

Heart rate reduction and cardiovascular risk reduction in man

Beta-blockers have been shown to reduce total mortality and sudden cardiac death after myocardial infarction. At least part of their beneficial effects has been ascribed to their effect on HR.19 Furthermore, a recent meta-regression of randomized clinical trials of beta-blockers and calcium channel blockers in post-myocardial infarction patients strongly suggests that the beneficial effect of these agents is proportionally related to resting HR reduction.20 A statistically significant relationship was found between resting HR reduction and reduction in cardiac death, all-cause death, sudden death, and non-fatal MI recurrence. Each 10 bpm reduction in the HR is estimated to reduce the relative risk of cardiac death by 30% (Figure 4). This meta-regression of the randomized clinical trials strongly suggests that resting HR reduction could be a major determinant of the clinical benefit in these trials. Recently, this hypothesis was tested within randomized controlled trials of beta-blockers in systolic CHF. There was a close relation between all-cause

![Figure 2](https://academic.oup.com/eurheartjsupp/article-abstract/10/suppl_F/F17/371647/371647)

**Figure 2** Mechanism of myocardial ischaemia as a mismatch between oxygen demand and oxygen supply by coronary blood flow.

![Figure 3](https://academic.oup.com/eurheartjsupp/article-abstract/10/suppl_F/F17/371647/371647)

**Figure 3** Role of heart rate in the development and progression of atherosclerosis (see text).

![Figure 4](https://academic.oup.com/eurheartjsupp/article-abstract/10/suppl_F/F17/371647/371647)

**Figure 4** Heart rate lowering is associated with reduction in cardiac deaths in post-myocardial infarction patients. From Cucherat.20
annualized mortality rate and HR. A strong correlation between change in HR and change in LV ejection fraction was also observed. These data suggest that HR reduction is indeed a major component of the prognostic benefit in post-MI and CHF trials with beta-blockers and therefore should be an important therapeutic goal for the improvement of prognosis.

The mechanisms by which HR influences the outcome has not been completely unravelled. It is well known that exercise training is associated with lower resting HR. In fact, exercise capacity was found to be a strong predictor of mortality. HR is also determined by the influence of the autonomic nervous system balance. The major effect of beta-blockers is HR reduction but other actions may operate. A significant proportion of patients with myocardial infarction or myocardial ischaemia do not receive beta-blockers, probably because the common occurrence of side effects or contraindication in patients with asthma, hypotension, and atrioventricular conduction disorders, together with their negative chronotropic effect, limit their use. Therefore, there is a need for developing new agents to obtain HR reduction in vast majority of patients.

Ivabradine is a new medication that has HR-lowering properties without other direct cardiovascular effects. Ivabradine is the first of a new class of agents that act specifically on the sino-atrial node by inhibiting the If current of cardiac pacemaker cells without affecting other cardiac ionic currents. Ivabradine has a unique pharmacodynamic profile as HR reduction is not associated with negative inotropic effects or vasodilation.

Ivabradine has been investigated in patients with stable coronary artery disease. A double-blind, placebo-controlled study in patients with chronic stable angina showed that ivabradine produced dose-dependent improvements in exercise duration and time to development of exercise-induced ischaemia. Ivabradine showed anti-anginal and anti-ischaemic efficacy compared with such well-established reference anti-anginal drugs, such as beta-blockers and calcium antagonists. Ivabradine was also found to have beneficial effects on cardiac remodelling, capillary density, and LV dysfunction.

Conflict of interest: none declared.

References


