How does Heart Rate Control Improve the Treatment of Heart Failure?

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Abstract

Elevated heart rate is associated with poor cardiovascular outcomes. The reduction of heart rate is one of the goals in the treatment of patients with heart failure and reduced ejection fraction. The studies that involve the use of ivabradine, a drug which acts solely by decreasing heart rate, have shown that this effect, per se, reduces the risk of hospital admission and death in these patients. This review examines the results of studies that show reductions in the rate of myocardial oxygen consumption and shear stress, as well as increase in myocardial perfusion related to the reduction of heart rate.

Keywords: heart rate control, Heart failure.

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Introduction

Reduction of heart rate (HR) is one of the goals of pharmacologic therapy of heart failure (HF) with reduced left ventricle ejection fraction (LVEF), mainly through the use of beta-blockers (carvedilol, metoprolol and bisoprolol). Randomized trials have shown that chronic blockade of beta adrenergic receptors improves symptoms, reduces hospitalization, and enhances survival, even though acute effects are often detrimental. In patients with chronic HF, heart rate can be measured easily, and appears to be both a marker of risk and a target for therapy. Although the HR is commonly associated with other risk factors for cardiovascular disease, in many multivariable analyses, the association of HR with cardiovascular morbidity and mortality is independent of traditional risk factors, mainly when it exceeds 70 bpm. This occurs probably because elevated HR decreases myocardial demands of oxygen and increases myocardial perfusion by reducing the time of diastole and, consequently, the time of the filling of the coronary arteries. Besides this, a high rate increases shear stress on the endothelium and in the endocardium, resulting in a chronic inflammatory response that accelerates atherosclerotic processes, and causes damage to myocytes (leading to apoptosis and hypertrophy), interstitial fibrosis, impaired beta-adrenergic signaling, arrhythmia promotion, and stimulation of other detrimental systems such as the renin-angiotensin-aldosterone axis.

An Independent Risk Factor

Elevated resting HR is associated with cardiovascular and all-cause mortality in patients with coronary heart disease and also in apparently healthy subjects from the general population. A prospective population study, with a follow-up time of 23 years, on more than ten thousand patients demonstrated that increased HR was significantly associated with death from all causes and with death from cardiovascular causes. During the first year, it was estimated that beta blocker therapy saved 3.8 lives per 100 patients treated, and was associated with four fewer hospitalizations per 100 patients treated. An Independent Risk Factor

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The BEAUTIFUL trial in turn, showed that HR is an independent prognostic risk factor in patients with stable coronary artery disease and left ventricular systolic dysfunction. In this study, patients with heart rates of 70 beats per minute (bpm) or more had 34% more risk for cardiovascular death, 53% more admission to hospital for heart failure, 46% more admission to hospital for myocardial infarction, and 38% more necessity of coronary revascularization. The increase in each of these risks was also observed with each increase of 5 bpm in the HR [8]. That is, in apparently healthy patients and also in those with established coronary and ventricular disease, elevated heart rate is a risk factor for cardiovascular or non-cardiovascular outcomes. In addition to being associated with other risk factors, HR alone is a prognostic factor. This is suggested by the beneficial effects of ivabradine, a selective inhibitor of the sinoatrial pacemaker modulating “f-current”, resulting in the reduction of sinus rate by prolonging the slow depolarization phase. In other words, this is an agent that acts solely by decreasing heart rate. The SHIFT trial enrolled 6558 HF patients with LVEF of 35 percent or less and a sinus heart rate of 70 bpm or more. This study found that ivabradine reduced a composite of cardiovascular death and hospital admission for worsening heart failure, and that this clinical benefit was associated with the reduction in heart rate [9].

Inflammation and Heart Rate

Recent data suggest that biomarkers of systemic inflammation, especially plasma levels of high sensitivity C-reactive protein and fibrinogen, can identify healthy subjects who have an increased risk of developing disease. Multiple evidence pinpoints inflammation as a key regulatory process that links multiple atherosclerosis risk factors with altered arterial biology [7]. In healthy patients, elevated levels of high sensitivity C-reactive protein are associated with the incidence of cardiovascular disease and mortality [8] and the incidence of cancer [9]. In the same way, plasma fibrinogen level is moderately to strongly associated with risk of coronary heart disease, stroke, cardiovascular and nonvascular mortality [10].

The immune system communicates with the autonomous nervous system. This interaction can be illustrated by the rich autonomic innervation of bone marrow and of the lymphatic system. Another example is that the stimulation of the efferent vagus nerve decreases heart rate and also inhibits the inflammatory response (by inhibiting the release of tumor necrosis factor and other cytokines from macrophages) through acetylcholine release in the reticulo-endothelial system. Elevated levels of inflammatory markers may affect autonomic balance. Interleukin-6, for instance, has been found to influence the autonomic balance of the brain by affecting the hypothalamic–pituitary–adrenal axis. Thus, impaired autonomic balance and inflammation may interact with each other [10-12].

The Copenhagen City Heart Study demonstrated that there was a positive association between resting heart rate and plasma levels of high sensitivity C-reactive protein and of fibrinogen. This study showed that the combination of increased C-reactive protein and of reduced HR variability was much more effective for identifying high-risk subjects than either of these two alone, characterizing a synergistic effect between them [13].

Shear Stress and Arterial Stiffness

Shear stress has a direct influence on the pathogenesis of atherosclerosis via regulation of endothelial cell function and integrity. It also influences many of the processes relevant to the development of the atherosclerotic lesion, including secretion of growth factors, regulation of coagulation, and transmigration of leukocytes [14]. So, reduced HR variability is probably a much greater contributor to the progression of coronary atherosclerosis than a consequence of severe ischemic heart disease. The elevated minimum heart rate during sleep hours was found to be related to the progression of coronary artery stenosis [15].

Turbulence in the blood flow and changes in shear stress have been shown to result in morphological changes in the vascular endothelial cells and in intimal thickening, thus promoting accumulation of atherogenic particles within the endothelium. Thus, the reduction of HR decreases the frequency of shear stress throughout the cardiovascular system. This may be one of the mechanisms that justifies the clinical benefits of the HR reduction. Beyond the interaction with the atherosclerosis pathogenesis, the elevated HR could also be associated with a greater possibility of the disruption of a pre-existing coronary plaque [16].

Another study also related HR to arterial rigidity. The degree of arterial distension and the velocity of the pulse wave were analyzed at different heart rates in normotensive and hypertensive subjects. It was proved that a higher heart rate was strongly associated with reduced distension and elevated pulse-wave velocity, even after adjustment for age and blood pressure [18]. This demonstrates a possible pathophysiological mechanism of the relationship between high blood pressure and HR, both independent risk factors for cardiovascular events.

Myocardial Ischemia

Elevated HR acts by increasing the myocardial demand for oxygen and by decreasing its perfusion. The first occurs because of the rise in the myocytes metabolism necessary for the acceleration of the heart pump and for the excitation-contraction coupling. The second occurs because perfusion happens predominantly during diastole, and the fraction of the cardiac cycle occupied by diastole increases significantly as HR decreases. Furthermore, in patients with coronary artery disease, transient myocardial ischemia induced by increased metabolic demand is not associated with maximal vasodilation, which occurs in healthy subjects in this situation. Rather, an inappropriate severe microvascular vasoconstriction is present [19]. Therefore, a high HR exacerbates myocardial ischemia in these patients.

Arrhythmias

As already discussed, the elevated HR is associated with sudden death from acute myocardial infarction [10]. A recent study quantified the deceleration of the HR through Holter-24 hours in post-infarction patients and concluded that impaired heart rate deceleration capacity is a powerful predictor of mortality after myocardial infarction. The deceleration capacity was even more accurate than LVEF and than the conventional measures of heart-rate variability [20].

Rate control in order to prevent rapid atrial fibrillation usually leads to an improvement in symptoms in patients with heart failure. This was demonstrated in the randomized United States Carvedilol Heart Failure Trial, that included patients with atrial fibrillation and with heart failure due to systolic dysfunction [21]. In addition, slowing the ventricular rate often leads to a moderate or, in some cases, to a marked improvement in left ventricular function [22, 23].

Ideal heart rate

Establishing an ideal heart rate band has been a challenge according to previous studies. The majority of these studies agree on a heart rate of 55-65 bpm in sinus rhythm as the best way to achieve the lowest
cardiovascular event rate with beta-blocker therapy [8]. However, during clinical practice, it is always necessary to observe the heart rate tolerated by each patient and to observe if the low HR of the patient is not associated with symptoms of dyspnea and syncope. Also, another difficulty to establish a unique HR for all individuals is that HR has been reported to decrease with age, increase in women, and variate throughout the day [26].

In patients with chronic heart failure with reduced ejection fraction and atrial fibrillation, the optimum heart rate is also controversial, but it is apparently higher than that for patients in sinus rhythm [22]. It is also important to emphasize that in patients with heart failure with preserved ejection fraction, the reduction of the heart rate can be deleterious [24].

**Drugs**

Beta-adrenergic blockers remain the first-line therapy for reducing heart rate by its sympathetic inhibition, though indirect actions, such as the modulation of beta-receptor expression and of the renin–angiotensin system through the prevention of renal renin release. The effect on the atrioventricular node slows the conduction at this level and is also responsible for lowering the ventricular rate in supraventricular tachycardias, most notably in atrial fibrillation (negative dromotropic effect). With this therapy the patient also recovers responsiveness to beta-adrenergic agonists due to the up regulation density and to the sensitivity of beta-1-receptor. In this way, the beta-blockers help to restore the inotropic and chronotropic responsiveness of the myocardium, thereby improving contractile function [22-28].

As well as the beta blockers, other drugs also act to reduce heart rate, such as ivabradine. As discussed before, it is a selective inhibition of a pacemaker-modulating current in the sinoatrial node [29]. Digoxin is another agent that can decrease HR. It acts inhibiting the membrane sodium–potassium ATPase, which promotes sodium–calcium exchange. The increase in intracellular calcium concentration mediates the positive inotropic effect of digoxin, and the stimulation of central vagal nucleus is responsible for the decrease in HR. Additionally, digoxin may reduce HR by reducing sympathetic nervous system activity [30].

Verapamil is a non-dihydropyridine calcium channel blocker that results in a negative chronotropic effect that may slow the sinus rate. Verapamil is also used to control HR in patients with atrial fibrillation or with atrial flutter [31]. Lastly, amiodarone is another drug that has a variety of effects including blocking potassium channels, thereby prolonging repolarization and reducing the HR [32].

This miscellaneous drug arsenal can be used in cases of beta-blocker intolerance or for treatment of heart rate not adequately controlled by the use of beta-blockers. In patients with heart failure or with coronary artery disease, which are in sinus rhythm, and with HR above 70 bpm despite beta-blockers, ivabradine appears a safe treatment to improve clinical outcomes. Digoxin is an option to control ventricular rate when combined with a beta-blocker in patients with HF with reduced ejection fraction and atrial fibrillation, but the optimal ventricular rate has yet to be established. This drug can also be used (always at low doses) in symptomatic HF patients with reduced LVEF, that are in sinus rhythm and that are intolerant to beta-blockers. Amiodarone may be an alternative to digoxin in this first indication. Verapamil might be beneficial in patients with HF with preserved ejection fraction, though data in this area are still sparse [33].

**Conclusion**

Elevated heart rate is an independent risk factor for both cardiovascular and non-cardiovascular events. Elevated HR increases mortality, morbidity and hospitalizations of patients with heart failure and reduced ejection fraction. In this article, we have shown several pathophysiological mechanisms that justify the clinical benefits of rate control, such as its relationship with inflammatory cytokines, atherosclerosis, arterial wall stiffness, arrhythmias, shear stress and myocardial ischemia. Therefore, the importance of heart rate control should be exalted, and more studies must be developed in order to determine optimal heart rate for heart failure patients and even for healthy people. Beta-adrenergic blockers remain the first-line therapy for reducing heart rate. Beta-blockers also help to restore the inotropic and chronotropic responsiveness of the myocardium and to improve contractile function. Ivabradine is another drug that is very helpful for controlling HR in patients in sinus rhythm. In heart-failure patients with atrial fibrillation, low dose Digoxin combined with a beta-blocker can be used to help control ventricular rate. Amiodarone can also be used in the same context. Verapamil could be an option in patients with HF with preserved ejection fraction.

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