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Review

Heart rate as a target of treatment of chronic heart failure

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ABSTRACT

Cardiovascular risk of increased heart rate (HR) was first reported in the Framingham study. Thereafter, the risk of increased HR for mortality has been extensively studied, suggesting the higher risk in clinical outcomes with increased HR in the general population and in patients with coronary artery disease or heart failure (HF). In a long-term follow-up study in Framingham, the general population in this cohort showed an increase in all-cause mortality by 14% at every 10 bpm increase in HR. In patients with heart failure, resting HR of more than 80 bpm could cause myocardial dysfunction which further deteriorates HF. Downregulation of β-adrenoreptor receptors with suppressed signal transductions, impaired intracellular Ca homeostasis, and excitation–contraction coupling may play a role in myocardial dysfunction. These subcellular alterations are mimicked in the pacing-induced HF in large animals; however, exact mechanisms of cardiac deterioration by increased HR are not fully understood. β-Blocker treatment is the most effective therapy for long-term survival of patients with chronic HF. Meta-analysis of HR reduction and improvement in survival in patients with chronic HF indicates that HR reduction is more important than the titrated dose of β-blockers, although the relative importance of HR reduction in improvement of prognosis is not clear. A recent study in which ivabradine decreased the hospitalization from HR deterioration in patients with chronic HF, demonstrated that further HR reduction with optimal treatment for HF is beneficial for clinical outcomes of the patients. These findings strongly suggest that HR reduction should be a pivotal target of the treatment in patients with HF.

Contents

1. Introduction

In healthy adult subjects, resting heart rate (HR) mostly ranges between 60 and 70 bpm, although it is proportionally lower with age. The mean HR is slightly higher in females than in males of the same age [1]. HR and blood pressure vary at every moment depending on physical activities and emotional conditions, mainly regulated by autonomic nerve activities through baroreceptor feedback loop. Therefore, HR is one of the biomarkers reflecting the sympathetic and parasympathetic activities.

It is of note that there are a number of reports which indicate that resting HR is inversely related to mortality in the general population without known or suspected heart diseases and in patients with ischemic heart disease or heart failure (HF) [2]. This association is most apparent in sudden death from myocardial infarction [3]. It is also reported that cardiovascular death is increased by 14% with an increase of 10 bpm in HR [4], and this increase in cardiovascular death is independent of age, exercise capacity, systolic blood pressure, body mass index, and physical activity in daily life [5]. In patients with chronic HF, resting HR is elevated in advanced HF. It is well known that the most effective drugs for chronic HF

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are angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor antagonists (ARB), and β-blockers, all of which reduce the HR in patients with chronic HF. Obviously, reduction of HR is a pivotal effect of β-blockers in prolongation of survival of HF patients. In this review, the roles of HR in progression of HF and treatment of chronic HF are discussed.

2. Increased HR and cardiovascular mortality

It has been extensively reported that increased HR is correlated with cardiovascular mortality in the general population and in patients with ischemic heart disease [2–5]. It is of interest that an inverse semilogarithmic relationship is observed between HR and life expectancy among mammalian species, except humans [6]. This relationship may suggest that the total number of heartbeats during a lifetime is constant among animals and HR is a marker of metabolic rate in individual animals.

The first report of the close relation between HR and mortality came from the Framingham study. Levy et al. reported that transient tachycardia alone or associated with transient hypertension is a prognostic risk factor in the general population [7]. In the following 30 years, they observed that overall and cardiovascular mortality rates were increased with resting HR in both sexes and all ages. Resting HR was an independent risk factor for survival even after adjustment for other risk factors, e.g. age, hypertension, serum lipid, smoking, and left ventricular hypertrophy [8]. The importance of resting HR as a risk factor for survival in the general population has been supported by other observational studies. In these studies, no ethnic differences were observed. Jouven et al. reported in a study of middle-aged working men that resting HR of more than 83 bpm is a risk factor for all-cause, non-sudden and sudden cardiac death from myocardial infarction [5].

There are also a number of reports in cohort studies for patients with coronary heart diseases. The CASS study (Coronary Artery Surgery Study) followed 24,913 patients with coronary artery diseases for 14.7 years, which showed that increased HR correlated with all-cause and cardiovascular mortality and hospitalization due to cardiovascular causes [9]. In this study also, resting HR of more than 83 bpm at the entry was a risk factor for all-cause and cardiovascular death even after multivariate analysis with several other cardiovascular risk factors. The INVEST study (International Verapamil-SR/trandolapril Study) included more than 22,000 patients with hypertension and coronary artery disease. The study revealed a significant correlation between resting HR and all-cause death, non-fatal myocardial infarction, and non-fatal stroke [10]. The mortality rate in patients with HR of above 100 bpm was more than double than in patients with HR of less than 100 bpm. In total cohort studies, resting HR correlated well with adverse outcomes despite a good control of blood pressure. In a recent study in which 1453 patients with acute myocardial infarction treated with percutaneous coronary recanalization were studied, resting HR of more than 78 bpm at discharge with adequate treatment including β-blockers, antiplatelet agents, ACE inhibitors/ARB, and statins was associated with higher one-year mortality than in patients with HR below 78 bpm [11]. In this study every increase of 5 bpm in HR was related with an increased mortality by 26%.

The relation between resting HR and clinical outcome was studied in the control arm of BEAUTIFUL (Morbidity–mortality Evaluation of the If Inhibitor Ivabradine in Patients with Coronary Disease and Left-ventricular Dysfunction) study in which an If channel inhibitor, ivabradine was evaluated in patients with coronary artery disease and LV dysfunction (LV ejection fraction ≤40%). More than 5000 patients in the control arm were divided into two categories; resting HR of ≥70 bpm and <70 bpm. In the higher HR group, cardiovascular mortality was greater by 34% and hospitalization was also higher by 53% compared with the lower HR (<70 bpm) group [12]. In this study, every 5 bpm increase was associated with increased cardiovascular death by 8% ($p = 0.005$) and increased rate of hospitalization due to HF by 16% ($p < 0.001$). This study clearly showed the close correlation of increased HR with progression of HF [12]. The SHIFT (Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial) study evaluated the effect of HR reduction with ivabradine on clinical outcomes in patients with chronic HF with HR of ≥70 bpm and LVEF of ≤35% [13]. The control arm in this study is very useful to investigate the clinical outcomes in relation to resting HR as observed in the BEAUTIFUL study. The subgroup with highest HR (≥87 bpm) showed a hazard ratio of 1.86 for all-cause death, 3.56 for HF death, and 2.99 for HF hospitalization compared with the subgroup with lowest HR (70–72 bpm). The primary composite endpoint was increased by 3% with every increase in HR by 1 bpm. This study also demonstrated that increased HR is a risk factor for cardiovascular death and HF progression in patients with chronic HF treated with a standard treatment including β-blockers.

3. Heart rate and HR variability in heart failure

Heartbeat is regulated by the excitation of pace maker cells in the sinus node which is under autonomic nerve control. In healthy subjects, HR and HR variability are influenced by intrinsic factors e.g. circadian rhythm and metabolic rate, and also with extrinsic factors such as physical activity, smoking, meals, and emotional stress [14]. Respiration rate and tidal volume are also independent regulators of HR and HR variability via autonomic nerve activity [15].

In healthy subjects, cardiac vagal nerve activity predominantly regulates HR at rest. If the cardiac vagal nerves are completely inhibited, intrinsic HR, usually higher than resting HR is manifested [16]. Predominant vagal control of resting HR in healthy subjects is clearly demonstrated by a minimal change in HR after β-blocker administration but a substantial increase in HR with atropine administration. In patients with HF, resting HR is increased due to sustained inhibition of vagal nerve activity and subsequent sympathetic augmentation [17]. HR variability is markedly attenuated in patients with advanced HF over 24 hours [18]. This is in contrast to the obvious circadian rhythm of the frequency component in HR variation in healthy subjects. Also, normal responses of high/low frequency components during exercise are not observed in patients with HF [19]. Enhanced sympathetic nerve activity in patients with HF is mainly derived from the impaired baroreflex and muscular neural reflex. Central vagal nerve activity is also attenuated [17]. It is well known that increased angiotensin II in HF attenuates the afferent vagal nerve activity from the baroreceptors [20]. Other neuropeptides, e.g. norepinephrine and neuropeptide Y also inhibit the neurotransmission at the vagal nerve terminals [21]. Consequently HR is increased and HR viability is attenuated in patients with HF.

As discussed, increased HR is an independent risk factor for death in patients with ischemic heart diseases [9–12]. However, the relation between increased HR and mortality in patients with HF is not as straightforward as observed in coronary artery disease. This may be due to the complex features of death from HF, a mixture of sudden death and death from pump failure; pump failure is proportionally increased with progression of ventricular dysfunction whereas cardiac sudden death is not proportional to severity of functional class.

4. Increased HR and progression of HF

Tachycardia-induced cardiomyopathy (TIC) is cardiac dysfunction caused by tachyarrhythmias. This abnormality is often

reversible with the normalization of HR [22]. TIC is associated with several tachyarrhythmias including atrial fibrillation, atrial flutter, incessant supra-ventricular tachycardia, and ventricular tachycardia [23]. Although the exact mechanisms of TIC are still unknown, plausible mechanisms include abnormal calcium handling, down-regulation of myocardial β1 receptors, depletion of myocardial energy stores, and chronic ischemia similar to stunning or hibernation [24]. TIC also occurs in association with underlying heart diseases, in which sustained tachycardia aggravates impaired systolic function. Conversely, lowering HR could restore the impaired LV function. Thus, treating tachycardia either with ablation or medications results in significant improvement in cardiac function [25]. In patients with atrial fibrillation, HR is recommended to be optimally controlled between 60 bpm and 80 bpm at rest and between 90 bpm and 115 bpm during moderate exercise [26], since sustained HR above 100 bpm may be harmful for the heart causing TIC which leads to cardiac dilatation associated with elevated ventricular filling pressures, eventually, resulting in heart failure with neurohormonal activation.

Experimentally, it has been demonstrated that atrial or ventricular rapid pacing at 240–280 bpm for 2 weeks in dogs could produce severe biventricular systolic dysfunction which resembles TIC in humans [27]. Cellular changes include loss of cardiomyocyte, cellular elongation, and myofibril misalignment, often associated with derangement of the extracellular matrix. Although coronary blood flow and flow reserve are reduced [28], there is no clear evidence of myocardial ischemia in this model. Myocyte hypertrophy and fibrosis at the tissue level are absent or less in TIC [29], resulting in restoration of cardiac function after termination of pacing. However, the rapid pacing model is associated with neurohormonal activation; plasma renin, angiotensin II, aldosterone, norepinephrine, natriuretic peptides, and endothelin are usually elevated. These neurohormonal activations could cause chronotropic stimulation. These are adaptive alterations, yet may directly affect myocardial performance by altering oxygen consumption and hemodynamics. In failing myocardium, β-adrenoceptors are desensitized and down-regulated, in which signal transductions are suppressed with decreased adenylate cyclase activity and increased levels of inhibitory G protein and G-protein related kinases (GRKs), although these alterations could not explain the increased HR in failing heart [30]. In rapid pacing animal models, pro-inflammatory cytokines e.g. tumor necrosis factor-α and interleukin-6 are increased. In an epidemiological study, it was reported that increased HR and reduced HR variability are associated with increased C-reactive protein concentration and leukocyte count in healthy middle-aged and elderly subjects [31]. Thus, increased HR may be related to chronic inflammation in failing hearts. The excitation–contraction (EC) coupling is also impaired. Redundant β1-adrenoceptor stimulation causes decreased Ca2+ uptake and augments the Ca leak with reduced ryanodine receptor binding and phospholamban protein [32]. It is reported that chronic HR reduction by an If channel blocker, ivabradine, improves systolic function associated with an increase in FKBP12/12.6 expression which could stabilize the EC coupling [33].

HR may also contribute to the progression of atherosclerosis in coronary artery disease. In cross-sectional studies, HR was a significant determinant of arterial stiffness in patients with hypertension [34]. Also in a longitudinal study, Benetos et al. have demonstrated that increased HR is a major risk factor for accelerated carotid-femoral pulse wave velocity [35]. Even without severe coronary narrowing, an increase in HR results not only in an increase in myocardial oxygen demands, but also a decrease in coronary flow supply. This imbalance may promote myocardial ischemia, arrhythmias, and ventricular dysfunction in patients with coronary artery disease and HF. In these conditions, endothelial dysfunction plays a major role in enhancing inflammation, platelet aggregation, and vasoconstriction through decreased eNOS expression and increased secretion of cytokines and pro-thrombotic molecules [36]. Increased HR has been shown to be associated with coronary plaque rupture and subclinical inflammation in middle-aged and elderly subjects [37]. Although the mechanisms by which HR contributes to plaque rupture are not clarified yet, Custodis et al. have demonstrated that HR reduction with ivabradine decreases plaque formation concomitantly with attenuated vascular oxidative stress and an improvement in endothelial function in ApoE−/− mice [38]. Although increased HR is not a simple marker for deteriorated clinical outcome, it may be a mediator for the enhanced pro-inflammatory activation which may lead to cardiovascular abnormalities.

5. HR reduction in treatment of HF

A number of previous studies demonstrated that reduction in HR plays a pivotal role in β-blocker treatment of chronic HF. In a recent meta-analysis of 35 studies, HR reduction is strongly correlated with mortality. Hazard regression model analysis showed that HR reduction of 5 bpm could provide 14% risk reduction in mortality in β-blocker treatment [39]. There is also a close correlation between HR reduction and improvement in LV ejection fraction [40]. Improved LV ejection fraction is accompanied by a decrease in LV volume, indicating that β-blocker treatment for a long-term period results in LV remodeling [41]. Thus, there is no doubt that HR reduction in β-blocker treatment for chronic HF mainly contributes to the clinical benefit in this treatment. Although there is a rough correlation between the dose of β-blocker and the HR reduction, "how much HR can be decreased" is more important than "how much dose can be uptitrated" to achieve the better clinical outcome [39]. In Japan, the doses of β-blocker for treatment for HF are much less in the USA and European countries; the recommended dose for standard therapy is 20 mg/day for carvedilol [42] and 5 mg/day for bisoprolol. In the J-CHF (Assessment of Beta-Blocker Treatment in Japanese Patients with Chronic Heart Failure) study, the small doses of carvedilol (2.5–20 mg/day) were evaluated in Japanese patients with chronic HF, in which we observed a comparable HR reduction with other major clinical trials [43]. In CIBIS II (Cardiac Insufficiency Bisoprolol Study II) study, the mean HR reduction was 9.8 bpm in the bisoprolol treated arm [44]. The CAPRICORN (Carvedilol Post-infarct Survival Control in LV Dysfunction) study is a large clinical trial in patients with LV dysfunction following myocardial infarction, most of the eligible patients were at New York Heart Association (NYHA) functional class I or II, in which carvedilol treatment provided 23% risk reduction in all-cause mortality [45]. In contrast, the COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) trial studied patients with advanced HF, mostly with NYHA functional class IV [46]. In the MERIT-HF (Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure) trial, moderate HF patients mainly composed of NYHA II–III and LV ejection fraction of less than 40% were studied [47]. In these clinical trials, bisoprolol for CIBIS II trial, carvedilol for COPERNICUS trial, and metoprolol CR/XL for MERIT-HF trial provided comparable clinical benefit; risk reductions in all-cause mortality were 38%, 35%, and 34%, respectively. Hospitalization due to worsening of HF was also attenuated with β-blocker treatment; risk reductions for HF hospitalization were 28% in the COPERNICUS study and 30% in the MERIT-HF study. In many countries all over the world, carvedilol, bisoprolol, and metoprolol CR/XL are widely used as β-blocker treatment for chronic HF based on the comparable clinical benefit in these clinical studies. In Europe, nebivolol is approved for clinical use for treatment of elderly patients with mild-to-moderate HF. Nebivolol is a β1 selective

antagonist without α1-blocking effect. This drug has a potent effect in HR and blood pressure reduction with 10-fold potency greater than atenolol [48]. In terms of HR reduction, bisoprolol, carevedilol, and nevibolol have comparable effects in HR reduction.

In healthy subjects, administration of β-blockers decreases the exercise capacity; 14% decrease with bisoprolol, 15% with carvedilol, and 13% with nebivolol [49]. However, exercise capacity is restored during long-term treatment with β-blockers [50]. In many studies the improvements in exercise time and myocardial oxygen consumption (MVO2) were demonstrated after several months of treatment with β-blockers, in which neurohormonal improvements e.g. B-type natriuretic peptide, endothelin-1, and inflammatory cytokines were also observed [51]. A decrease in exercise capacity during short-term treatment with β-blockers is mainly due to chronotropic incompetence during exercise [52]. In long-term treatment, however, the chronotropic incompetence with β-blocker is minimally observed, in which neurohormonal improvement may in part contribute to this improvement. One meta-analysis also showed an improvement in 6-min-walk distance with β-blocker treatment which is greater in patients with severe HF [53]. From these findings, β-blocker treatment demonstrates that HR reduction is accompanied by improvement in physical capacity and NYHA functional class, and survival of the patients with HF.

Recently, a selective HR lowering drug which does not affect hemodynamics and sympathetic modulation, an If channel inhibitor, has become available for treatment of chronic HF in Europe. In BEAUTIFUL (Morbidity–mortality Evaluation of the If Inhibitor Ivabradine in Patients with Coronary Disease and Left-ventricular Dysfunction) study, ivabradine was tested in 10,917 patients with LV dysfunction due to coronary heart disease [54]. During 12-month treatment, HR decreased 6 bpm from baseline HR (71.6 bpm), however, ivabradine did not improve the primary endpoint, the composite of cardiovascular death, hospitalization from acute myocardial infarction and HF hospitalization [54]. Since subanalysis of the patients with HR of ≥70 bpm indicated some favorable effects, the SHIFT trial was undertaken in 6505 patients with chronic HF who had LV dysfunction (LV ejection fraction ≤35%) and higher HR of 70 bpm [13]. Ivabradine decreased HR as much as 10.9 bpm with a significant reduction in primary endpoint by 18%. It is of note that the decrease in the primary endpoint was mainly attributable to a decrease in hospitalization due to HF deterioration (HR 0.74) whereas a reduction in cardiovascular death was minimal (HR 0.91). These results may indicate that ivabaradine minimally inhibits sudden death but substantially attenuates progression of HF. It is important to notice that these clinical benefits were obtained under the optimal treatment of β-blocker (90%), ACE-inhibitor (80%)/ARB (14%), and aldosterone antagonists (60%) [13]. In this study, hospitalization with HF deterioration was decreased by 26% in association with HR reduction of 11 bpm. From these results, we can conclude that ivabradine is effective for the additional HR reduction to β-blocker's effects, which could further decrease a risk of HF progression.

Another HR control treatment is atrial pacing with concomitant administration of a large dose of β-blockers or ablation of atrioventricular node. Thackray et al. showed that pacing at the rate of 80 bpm for 14 months deteriorated LV function compared with pacing at 60 bpm [55]. Taken together, it can be concluded that HR reduction by β-blockers or other means is critically important in improvement in clinical outcomes of HF patients.

6. Conclusion

HR is mainly regulated by autonomic nerve activities; resting HR is increased with attenuated vagal nerve activity or enhanced sympathetic nerve activity. In the general population and in patients with coronary heart disease or HF, increased HR is inversely correlated with all-cause or cardiovascular mortality. Although the precise underlying mechanisms of these abnormalities with increased HR are not yet clarified, numerous clinical and experimental evidence suggests that HR is related to atherosclerosis of the vessels, plaque rupture, and vascular inflammation as well as dysregulation of intracellular Ca homestasis, EC coupling, and β-adrenoceptor signal transductions in cardiomyocytes and cell death in the myocardium. Some evidence also suggests that beneficial effects of β-blockers on long-term survival of patients with chronic HF could be largely contributed to HR reduction with this drug. It is strongly supported by the finding that improvement in survival is closely correlated with HR reduction but not with the dose of β-blockers in treatment of HF. Ivabradine, a selective HR-lowering drug further improved clinical outcomes, supporting the pivotal role of HR in pathophysiology and treatment of chronic HF. However, the clinical significance of increased HR in sudden death in patients with HF is to be elucidated.

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