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Heart Rate as a Therapeutic Target for the Prevention of Cardiovascular Disease

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Abstract

Evidence from epidemiologic studies demonstrates that resting Heart Rate (HR) is an independent risk factor for Cardiovascular (CV) event. In addition, recent studies indicate that follow-up HR adds prognostic information over and above baseline HR. Elevated resting HR represents sympathetic over-activation leading to cardiometabolic deterioration and is also associated with subclinical inflammation and target organ damage. In addition, elevated resting HR might modify the local hemodynamic environment and contribute to atherosclerosis formation. A pure HR-lowering drug, Ivabradine, reduces CV event in patients with coronary artery disease and chronic heart failure. These findings indicate that elevated resting HR is not just as an epiphenomenon representing "poor conditioning" but a therapeutic target. The potential role of HR and its modulation should be considered in the future guidance documents.

Keywords: Heart rate; Beta-blocker; Cardiovascular disease

Introduction

Based on extensive evidence from epidemiologic studies and clinical trials designed for other purposes, elevated resting Heart Rate (HR) is an undesirable prognostic sign. The BEAUTIFUL [1] and the SHIFT [2] studies, however prospectively evaluated the prognostic significance of lowering resting HR and demonstrated that resting HR should be a therapeutic target for patients with CAD and chronic heart failure. However, physicians have considered elevated resting HR to be an epiphenomenon representing "poor conditioning". In this review article, we summaries the clinical significance of elevated resting HR and discuss the clinical applications of follow-up HR for the improvement of patient prognosis.

Resting HR as a Prognostic Factor

That elevated HR is a risk factor of all-cause and CV mortality within a wide spectrum of subjects is supported by numerous epidemiological studies [3]. Elevated resting HR has been considered as a risk factor for undesirable prognosis independent of confounding factors. Elevated resting HR is a common feature among patients with hypertension. The Framingham study [4] demonstrated that each increment in resting HR of 40 bpm doubled the risk of death both hypertensive men and women. In the placebo arm of the Syst-Eur trial [5], patients with resting HR>79 bpm had approximately twice greater risk of all-cause mortality and a 1.6 times greater risk of CV mortality than the subjects with HR below that level.

Recent studies indicate that follow-up HR adds prognostic information over and above baseline HR (Table 1). In the general population and male healthy workers, an increase in follow-up HR increased mortality risk [6,7]. Among these studies, the Paris Prospective Study 1 [6] demonstrated the valuable findings. They followed a total of 5,139 healthy working men and showed increase in follow-up HR had a 19% increased mortality risk (95%CI 1.04-1.37). They also demonstrated that decrease in follow-up HR of at least 4 bpm had a 14% lower mortality risk (95% CI: 0.74–1.00). The association between follow-up HR and adverse outcome is also demonstrated in hypertensive patients [8-12]. The Glasgow Blood Pressure Clinic Study [8] demonstrated developing or persistent resting HR>80 bpm increased the risk of all-cause (hazard ratio: 1.78, 95% CI: 1.31-2.41) and CV mortality risk (hazard ratio: 1.92, 95% CI: 1.24-2.99). In the LIFE study [9], a 10 bpm HR increase was associated with a 25% increased risk of CV mortality, and persistence or development of a follow-up HR>84 bpm was associated with an 89% greater risk of CV mortality. The association between follow-up HR and CV events was also found in other hypertensive studies regardless of the β-blocker use [10-12]. In patients with stable CAD, the increased CV event risk was apparent in patients with a mean follow-up HR>75 bpm, and the relationship between follow-up HR and event risk was not linear but J-shaped with a nadir at 59 bpm [13] (Figure 1). The follow-up HR may represent altered subjects' risk status such as cardiometabolic risks and overall hemodynamic stress on the arterial trees over time. Accordingly, clinical significance of follow-up HR is more evident than measured HR at baseline.

Resting HR and Comorbid Risk Factors

Individuals with tachycardia often have characteristic features of insulin resistance syndrome, including high blood pressure, obesity, increased blood glucose and insulin levels, and an abnormal lipid profile [14,15]. Moreover, an increase in the resting HR may predispose to these cardiometabolic abnormalities [16-18], suggesting that an early rise in sympathetic drive may promote these metabolic changes. Accordingly, elevated resting HR is not just an epiphenomenon of a subject's present cardiovascular risk. We examined the relationship between resting HR and cardiometabolic risks of approximately 10,000 healthy individuals. Elevated resting HR was associated with the number of cardiometabolic risks [15] and developing metabolic syndrome [18]. Elevated resting HR and sympathetic over activation found in masked hypertension and white coat hypertension are also consistent with this finding [19,20].

Elevated resting HR is also associated with subclinical inflammation.

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				HR		
Study name	**Patients**	**No.**	**Follow**	**Baseline**	**In-treatment**	**Results**
INVEST (16)	CAD with HT	22,576	2.7 y	75.7 75.7	69.2 72.8	CV event risk was apparent in patients with HR >75 bpm. J-shape HR and events relation was observed.
ASCOT-BPLA (45)	HT without CAD	12,759	3.8 y	At 73.8 Am 73.8	-12.0 -1.3	HR at 6 weeks was associated with the nonfatal MI and fatal CHD outcome.
Paris Prospective Study 1 (9)	Male healthy workers	5,139	23 y	N/A	N/A	Total mortality HR decrease vs. no change: RR 0.86 (95% CI 0.74-1.00) HR increase vs. no change: RR 1.19 (95% CI1.04-1.37)
VALUE (15)	High risk HT	15,245	4.2 y	Val 72.3 Am 72.5	N/A N/A	CV event Highest HR quintile vs. 4 lower HR quintiles: HzR 1.52 (95% CI: 1.36–1.69)
LIFE (12)	HT	9,190	4.8 y	At Los	-4.1 -0.5	Every 10 bpm increase CV mortality: HzR 1.16 (95% CI 1.06–1.27) Total mortality: HzR 1.25, 95% CI 1.17–1.33 Developing or persist >84bpm CV mortality; HzR 1.55 (95% CI 1.16–2.05) Total mortality; HzR 1.79 (95% CI 1.46–2.21)
ONTARGET / TRANSCEDENT (14)	High risk HT	31,531	5 y	68.0	N/A	Every 10bpm increase Total mortality: HzR 1.35 (95% CI 1.30-1.40) CV mortality: HzR 1.36 (95% CI 1.32-1.45) MCE: HzR 1.26 (95% CI 1.22-1.30) MI: HzR 1.03 (95% CI 0.97-1.03) Stroke: HzR 1.17 (95% CI 1.10-1.25)
Glasgow BP Clinic study (11)	Outpatient HT	4,065	2.5 y	77	74	Total mortality Persistent >80bpm vs. persistent <60bpm: HzR 1.78 (95% CI 1.31-2.41) CV mortality Persistent >80bpm vs. persistent <60bpm: HzR 1.92 (95% CI: 1.24-2.99)
Nord-Trøndelag County Health Study (10)	General population	29,325	12 y	N/A	N/A	Total mortality >85 vs. <70bpm: HzR 1.9 (95% CI 1.0-3.6) >85 vs. 70-85bpm: HzR 1.8 (95% CI 1.2-2.8)

BPM: Beats Per Minute; BP: Blood Pressure; CAD: Coronary Artery Disease; HzR: Hazard Ratio; RR: Relative Risk; CI: Confidence Interval; CV: Cardiovascular; HR: Heart Rate; HT: Hypertension; MI: Myocardial Infarction; MCE: Major Cardiovascular Events; N/A: Not Available; Y: years; At: Atenorol; Los: Losaltan; Am: Amlodipine

Table 1: Studies demonstrating the association between in-treatment HR or serial HR change and adverse outcome.

In the subjects without apparent coronary artery disease, resting HR and/or HR variability were associated with an increased CRP level and white blood cell count [21-23]. The RISC study [22] showed that white blood cell count and erythrocyte sedimentation rate were positively associated with an elevated resting HR, even after adjusting for confounding factors. Elevated resting HR is also associated with target organ damage such as microalbuminuria, chronic kidney disease, microvascular complication, and arterial stiffness [24-27] suggesting that resting HR is associated with all stages of cardiovascular continuum.

Cause and Pathophysiological Mechanism

Heart rate is genetically transmitted and the hereditability of HR is estimated to be approximately 21to 26% [28,29]. Heart rate was associated with a Ser49-to-gly (S49G) polymorphism in the beta-1 adrenergic receptor independent of other variables [30]. Of course resting HR is affected by numerous environmental factors, including psychological stress, fever (18 beats per degree Celsius), anemia, dehydration, and dietary pattern. Excessive intake of high-calorie diet rich in processed carbohydrates and saturated fat can lead to transient postprandial spikes in blood glucose, free fatty acids and triglycerides [31,32]. These conditions generate free radicals and trigger biochemical cascades of nitric oxide degeneration, inflammation, endothelial dysfunction, sympathoexcitation, parasympathetic depression, and a concurrent HR elevation [33-37]. These findings indicate that a lifestyle-induced increase in sympathetic drive may promote these cardiometabolic changes. It is plausible that elevated resting HR coexists with cardio-metabolic deterioration such as insulin resistance [38], blood pressure elevation [39] and risk accumulation [14,18]. In addition, elevated resting HR is also derived from blunted sensitivity of baroreceptor. Sympathetic overactivation that characterizes the heart failure syndrome can be found in the early phase of this condition. It is usually coupled to an impairment of the normal inhibitory baroreceptor modulation of central sympathetic outflow [35,36].

Elevated resting HR increases myocardial oxygen demand resulting in myocardial ischemia [40], and triggers serious ventricular arrhythmia [41]. In addition, elevated resting HR might modify the local hemodynamic environment and contribute to the development of atherosclerosis. In regions of the vasculature where flow reversal or shear oscillation is dominant, elevated resting HR is associated with expanded periods of low shear stress, potentially facilitating atherosclerotic lesion formation [42]. The inflammatory transcripts of endothelium is suppressed under physiological, but reversed at higher frequency of pulsatile flow, most pronounced under reversing and oscillatory shear [43]. Whereas, ivabradine improves endothelial function, reduces vascular oxidative stress and developing

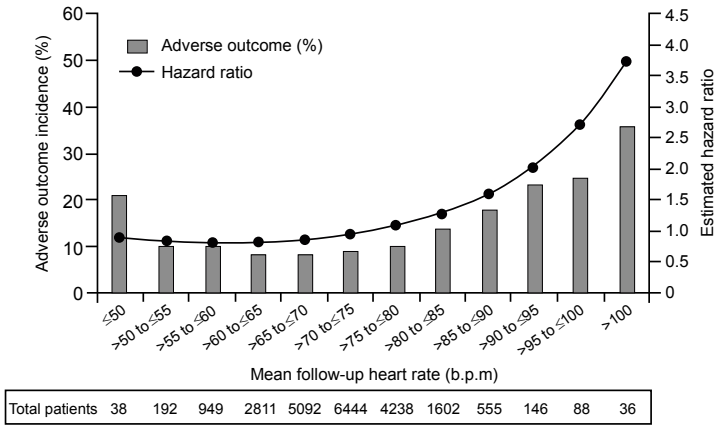

Figure 1: Relationship between in-treatment HR for INVEST patients and incidence of adverse outcomes (left axis, bars) and risk (right axis -●-, hazard ratio) derived from a stepwise Cox proportional hazards model. The nadir for in-treatment HR was 59 bpm. Reprinted with permission from Kolloch et al. (13).

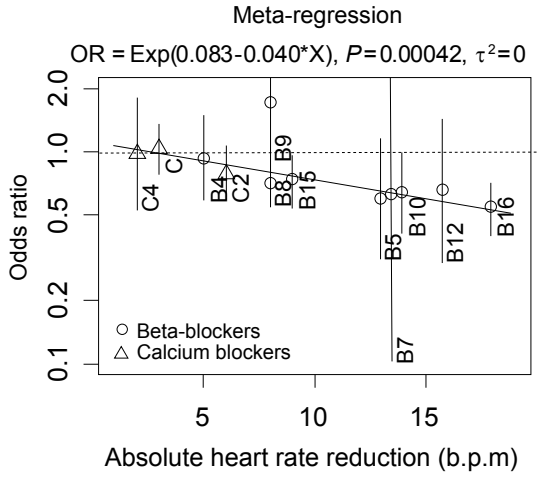

Figure 2: Relationship between absolute heart rate reduction and cardiac death in patients with post myocardial infarction. Reprinted with permission from Cucherat (54).

atherosclerosis in apolipoprotein E deficient mice [44]. The rate limiting by sino-atrial node ablation also retards atherosclerosis formation in cynomolgus monkeys [45,46].

Pharmacologic HR Lowering and Outcome

It is logically plausible that HR reduction leads to a better prognosis [6,8]. Non-pharmacologic HR lowering, such as dietary supplementation with omega 3 fatty acids [47], docosahexaenoic acid [48], exercise training [49], body weight reduction [50,51], and lipid lowering by HMG-CoA reductase inhibitors [52] also reduces HR and leads to favorable outcomes. In patients with heart failure and myocardial infarction, mortality reduction is evident with HR lowering [53,54]. The meta-regression analysis revealed that larger resting HR reduction was associated with a greater mortality reduction for cardiac death, all-cause death and sudden death in patients with post-myocardial infarction regardless of the therapeutic strategies (Figure 2). However, there are few evidences that demonstrated the clinical advantage of HR lowering in patients with stable CAD [13,55-59] (Table 2). Although none of these studies was designed for HR lowering as a therapeutic target, HR lowering with β-blocker reduced CV event rate. Although the APSIS [59] and the INVEST [13] did not show the prognostic significance between the therapeutic strategies, follow-up HR was associated with patients' prognosis regardless of therapeutic strategies [13]. In the INVEST, CV event risk was apparent in patients with resting HR>75 bpm [13]. Whereas, Bangalore et al. demonstrated in their meta-regression analysis that β-blocker-associated HR reduction increased the risk of CV events and death for hypertensive patients [60]. Their results, however, should be cautiously interpreted. The blood pressure of patients assigned to β-blocker was at most 9.2mmHg higher than control group in five out of seven active control studies. The CAFÉ study also suggested that an increase in central aortic pressure due to HR lowering might be the cause of increased CV event in β-blocker based strategy [61]. In the ASCOT-BPLA study, however, resting HR at 6 weeks was associated with the nonfatal myocardial infarction and fatal CHD outcome [10]. Accordingly, these results simply indicated that β-blocker was inferior to other drugs for blood pressure lowering, but not the deleterious effect of HR lowering. We have to pay attention to the rate of HR change and the dosage of β-blocker, because acute administration of higher-dose β-blocker for achieving HR and BP lowering result in greater risk than benefit [62,63].

The sympathetic inhibition has been identified as a potential effect

					HR		
Study name	**Patients**	**No.**	**Follow**	**Drug**	**Baseline**	**In-treatment**	**Results**
ASIST (34)	Silent ischemia	306	0.9 y	Ate Pla	75 75	63 75	All-cause death and CV events: RR 0.55, 95% CI 0.22-1.33 Aggravation of angina: RR 0.35, 95% CI 0.17-0.72 Adverse outcome: RR 0.44, 95% CI 0.26-0.75
BIP (35)	DM with CAD	2,723	3 y	BB Non BB	70 75	N/A N/A	Total mortality: RR 0.58, 95% CI 0.44-0.77 Cardiac mortality: RR 0.66, 95% CI 0.46-0.94
TIBBs (36)	Stable CAD	317	1 y	Bis Nif	74.2 74.0	N/A N/A	CV events rate: Bis 22.1% vs. Nif 33.1%, p=0.033
TIBET (37)	Stable CAD	682	2 y	Ate Nif Com	N/A N/A N/A	-15.4 +2.9 -13.5	No difference in adverse outcome among the strategies
APSIS (38)	Stable CAD	809	3.4 yrs	Met Ver	N/A N/A	N/A N/A	All-cause death: OR 0.94, 95% CI 0.53-1.67 All-cause death and CV events: OR 1.22, 95% CI 0.95-1.56
INVEST (16)	Stable CAD	22,576	2.7 y	Ate Ver	75.6 75.5	69.2 72.8	No adverse outcome difference between the drugs. CV event risk was apparent in patients with HR >75 bpm. J-shape HR and event relation was observed.

Ate: Atenolol; BB: β-blocker; Bis: Bisoprolol; CAD: Coronary Artery Disease; CI: confidence interval; Com: Combination; CV: Cardiovascular; DM: diabetes Mellitus; IHD: Ischemic Heart Disease; Met: Metoprolol; MI: Myocardial Infarction; N/A: Not Available; Nif: Nifedipine; NS: Not Significant; Pla: Placebo; RR: Elative Risk; Ver: Verapamil

Table 2: Studies demonstrating the association between rate-limiting therapy using β-blocking agents and the prognosis of patients with stable CAD. The effect of risk reduction using β-blocking agents are shown in the table.

of β-blocker, thereby, confounding factor for the association between resting HR and CV event reduction. Studies using ivabradine, which acts specifically on the sino-atrial node by inhibiting the If current of cardiac pacemaker cells, reinforced the clinical significance of lowering HR. The BEAUTIFUL trial [1] evaluated the stable CAD patients with reduced cardiac function with appropriate medical treatment including β-blocker and demonstrated HR lowering, but not ivabradine use itself, improved the coronary event in a subgroup of patients with a resting HR>70 bpm. This result shows the prognostic significance of HR reduction even in patients with stable CAD. Another ivabradine study, the SHIFT trial [2], evaluated the symptomatic chronic heart failure patients with guideline-recommended medical treatment and indicated that patients with achieved HR<60 bpm on treatment had fewer CV events than patients with an elevated resting HR. These results showed the clinical benefit of HR lowering in addition to appropriately treated patients and indicated that resting HR is a therapeutic target.

Resting HR is an established index for predicting the risk of patients with acute coronary syndromes and several risk scales have been developed [64-68]. In the long-term therapeutic strategy of stable CAD patients, however, most physicians ignore the significance of resting HR in spite of numerous evidences. CLARIFY [69], a real-world large international prospective observational registry of stable CAD patients, has been carried out to determine the long-term prognostic determinants in CAD, including resting HR. Moreover, "Heart rate Guide" is due to be published preceding the guidance documentation for HR [70] The "optimal resting HR level" might be a therapeutic option and contribute to reducing residual risk [71]. HR-guided patient care in addition to modification of the other cardiometabolic risks contribute to a better prognosis for the prevention of CV events [72].

Conclusion

As resting HR is a target for the prevention of CV events, the clinical importance of resting HR should be emphasized. HR-guided patient care allows ready-to use and cost-effective CV risk reduction.

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