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Pharmacological heart rate lowering in patients with a preserved ejection fraction—review of a failing concept

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Abstract Epidemiological studies have demonstrated that high resting heart rates are associated with increased mortality. Clinical studies in patients with heart failure and reduced ejection fraction have shown that heart rate lowering with beta-blockers and ivabradine improves survival. It is therefore often assumed that heart rate lowering is beneficial in other patients as well. Here, we critically appraise the effects of pharmacological heart rate lowering in patients with both normal and reduced ejection fraction with an emphasis on the effects of pharmacological heart rate lowering in hypertension and heart failure. Emerging evidence from recent clinical trials and meta-analyses suggest that pharmacological heart rate lowering is not beneficial in patients with a normal or preserved ejection fraction. This has just begun to be reflected in some but not all guideline recommendations. The detrimental effects of pharmacological heart rate lowering are due to an increase in central blood pressures, higher left ventricular systolic and diastolic pressures, and increased ventricular wall stress. Therefore, we propose that heart rate lowering per se reproduces the hemodynamic effects of diastolic dysfunction and imposes an increased arterial load on the left ventricle, which combine to increase the risk of heart failure and atrial fibrillation. Pharmacologic heart rate lowering is clearly beneficial in patients with a dilated cardiomyopathy but not in patients with normal chamber dimensions and normal systolic function. These conflicting effects can be explained based on a model that considers the hemodynamic and ventricular structural effects of heart rate changes.

Keywords Heart rate · Hypertension · Heart failure · Adrenergic beta-antagonist

Introduction

Based on epidemiological data and inferences from heart failure (HF) trials, most physicians believe that higher heart rates (HR) have deleterious effects over the long term. It is therefore a widely held assumption that interventions that lower HR can also improve cardiovascular outcomes in patients without heart failure. In this paper, we will briefly discuss the epidemiological results and critically evaluate the clinical and experimental effects of pharmacological HR lowering, with a focus on hypertension (HTN) and HF. We follow this with a brief discussion of the clinical outcomes of HR lowering in coronary artery disease and then attempt to reconcile the hemodynamic and ventricular structural effects of HR.

Data sources

To identify relevant articles, we searched MEDLINE (via PubMed) and the world wide web using search engines that use ranking algorithms based on importance, e.g., PageRank, until June 2017. We used Medical Subject Headings (MeSH) and key words, focusing on the most relevant terms, e.g., heart rate AND adrenergic beta-antagonist AND blood pressure OR central hypertension. We also manually searched pertinent reports to find additional relevant citations missed in our original search.

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Epidemiology—higher heart rates are prognostically unfavorable

A significant association between elevated resting HRs and mortality in patients with and without cardiovascular disease has been documented consistently since the 1980s and has been reviewed in detail elsewhere [1]. This has been demonstrated in population studies but also in patients with various cardiovascular diseases including HTN and HF. In the vast majority of these studies, an elevated HR was shown to be a strong and independent predictor of mortality. In one striking example, a 2005 report of 5713 previously healthy men without known or suspected heart disease, resting HRs above 75/min, increased the risk of sudden death by almost fourfold and all-cause mortality by twofold [2].

Pharmacology of heart rate lowering

Commonly used drugs that lower HR include beta blockers (ßBs), non-dihydropyridine calcium channel blockers, and ivabradine. All of these agents inhibit sinus node activity. The HR lowering effects of ßBs are mediated through reduced activation of ion channels while those of calcium channel blockers are induced by a calcium-dependent slowing of cellular depolarization of the pacemaker cells of the sinus node [3–5]. Calcium channel blockers and ßBs have a number of other cardiovascular effects besides HR lowering. Ivabradine slows the depolarization of pacemaker cells by inhibiting a mixed sodium and potassium channel (I_f channel) which is highly expressed in the sinus node [3, 6, 7]. Ivabradine is thus the only available drug that selectively reduces HR without other cardiovascular effects. Because of their declining use, we will not discuss digitalis glycosides, which are believed to lower HR by a neurohumorally mediated mechanism [8].

Heart rate lowering in hypertension—from recommendation to concern

No study has evaluated the long-term effects of pharmacological HR lowering drugs in healthy subjects. Some insights into the effects of HR can be gained from the many clinical studies of ßBs for treatment of uncomplicated HTN. It is important to recognize that atenolol was the predominant drug used in these studies. Since the introduction of ßBs in 1964, the proposed principal mechanism of action has been a reduction in HR and myocardial contractility, which is a universal feature of ßBs [9]. The decrease in peripheral blood pressure (BP) is the primary reason why ßBs have been promoted for use in HTN.

In this context, it is of interest to first review trends in guideline recommendations for the use of ßBs for HTN. Treatment recommendations have gradually but dramatically changed over the last two decades. In the 1997 Joint National Committee guidelines on prevention, detection, evaluation, and treatment of high blood pressure (JNC 6), ßBs or diuretic agents were recommended as first-line therapy for uncomplicated hypertension [10]. In 2003, JNC 7 was published, which recommended ßBs as optional first-line therapy in Stage 1 hypertension or in a two-drug combination for Stage 2 hypertension [11]. Safety concerns for ßBs in hypertension were first expressed in JNC 8 in 2014: "…the panel did not recommend β-blockers for the initial treatment of hypertension because in one study use of β-blockers resulted in a higher rate of the primary composite outcome of cardiovascular death, myocardial infarction, or stroke compared to use of an angiotensin receptor blocker, a finding that was driven largely by an increase in stroke" [12]. These concerns were raised in the landmark LIFE trial where the rate of the composite primary endpoint was about 13% higher in the atenolol group, resulting in an adverse outcome in about 1 in 50 patients [13]. The evolution of HTN guideline documents reveal waning expert support and even concern for using ßBs. Importantly, there has never been any randomized, placebo-controlled trial that demonstrated that ßBs reduce mortality in HTN. Notwithstanding, patients with HTN continue to be treated with atenolol, many for decades.

It is notable that the treatment protocol for the recently published SPRINT trial that demonstrated a marked reduction in fatal and nonfatal major cardiovascular events when a systolic blood pressure target of 120 mmHg was compared to 140 mmHg recommended ßBs for only one group of patients: "The protocol encouraged, but did not mandate, the use of drug classes with the strongest evidence for reduction in cardiovascular outcomes, including thiazide-type diuretics (encouraged as the first-line agent), loop diuretics (for participants with advanced chronic kidney disease), and beta-adrenergic blockers (for those with coronary artery disease). Chlorthalidone was encouraged as the primary thiazide-type diuretic, and amlodipine as the preferred calcium-channel blocker" [14]. Remarkably, this treatment strategy, which avoided HR lowering in the majority of patients, resulted in a 38% reduction in incident HF in patients with the lower blood pressure target, consistent with a powerful relationship between HTN and HF. In contrast, JNC 8 continues to endorse the use of the HR-lowering drug diltiazem, based on a trial that reported similar outcomes as a ßB cohort [15]. In light of the previous discussion, this recommendation should provide little reassurance as this comparison may suffer from concealed inferiority in both treatment arms.

It is frequently argued that ßBs are a heterogeneous class of agents with variable pharmacokinetics, bioavailability, and systemic vascular, and central nervous effects, and that much of the unfavorable data were gleaned from studies employing non-vasodilating, traditional ßBs such as atenolol. However,

essentially all clinically used ßBs reduce basal HR in a dose-dependent fashion, typically by 5 to 20 bpm [16]. In light of the emerging concerns about ßbs in HTN, it appears unlikely that "vasodilator ßbs" such as carvedilol or nebivolol will ever be systematically tested against more potent agents such as chlorthalidone.

Importantly, a meta-analysis of 22 randomized HTN trials that tested various ßBs in a total of more than 64,000 patients actually demonstrated that ßB treatment increased the risk of cardiovascular events in a HR-dependent manner; the lower the HR, the greater the risk for all-cause mortality, cardiovascular mortality, myocardial infarction, stroke, and heart failure [16]. Consideration of these findings argues against the widespread use of ßBs. However, the opposite has occurred. Between 1999 and 2012, the use of non-cardioselective ßBs in the USA has more than doubled and the use of cardioselective ßBs has increased by about 75% making them some of the most frequently prescribed medications [17]. At present, about 11% of US adults are taking ßBs. This compares to a disease prevalence of 29% for hypertension, 6% for coronary artery disease, and 1% for HF with a reduced ejection fraction [18].

There is an emerging recognition that HR lowering has unfavorable hemodynamic effects. HR lowering can result in central blood pressure elevation even as the peripheral blood pressure is reduced. The increase is the result of reflected systemic arterial pressure waves that potentiate central blood pressures as demonstrated in the CAFE substudy of the ASCOT trial [19]. This HTN trial compared atenolol combinations versus amlodipine combinations that resulted in identical peripheral blood pressures. However, central systolic and diastolic blood pressures were 4.3 and 1.4 mmHg higher in the atenolol group, in whom HR was lowered by an average of 11 bpm. That this observation is ascribable to the lower HR is consistent with a recent ivabradine report [20]; as discussed above, this drug does not have vascular effects. In this study, ivabradine reduced the average HR by 9 bpm and increased the central systolic blood pressure by 11 mmHg without changing peripheral blood pressures. The investigators also reported an increase in LV stroke volume due to a prolonged LV filling time, which increases LV preload. These studies demonstrate that pharmacological HR lowering can increase LV wall stress, which may explain why ßb-treated patients were found to have up to a twofold increase in brain natriuretic peptide (BNP) levels in historic observational HTN studies [21, 22]. In resting patients with normal ejection fraction, lower HRs cause higher left atrial pressures, at least in part due to a prolonged filling time, as demonstrated in Fig. 1. This poorly appreciated finding is counterintuitive to many physicians because HR elevations with physical exercise have been associated with higher LV filling pressures [23]. However, it is well documented that atrial pacing in fact decreases LV end-diastolic pressure in resting patients with a normal ejection fraction [24–26]. It could therefore be argued that sedentary patients on HR-lowering medications who spend most of their time at their resting HR are most prone to sustained elevations in atrial and LV filling pressures.

In summary, acute and chronic pharmacological HR lowering results in elevated central blood pressures even though peripheral blood pressures can be lower.

The beneficial effects of heart rate lowering in heart failure with a reduced ejection fraction—revival of a paradigm

Due to initial concerns about the negative inotropic effect of ßbs, it took more than 20 years for their widespread clinical adoption in heart failure with reduced ejection fraction (HFrEF) patients. When the mortality reduction of ßBs is compared to other effective drugs for HFrEF, they are the most efficacious class [27]. It is informative to review the trajectory of mechanistic explanations in regard to why ßbs are beneficial and realize that the "HR-hypothesis" has fallen in and out of favor over time. In the first report of the use of ßbs in patients with congestive heart failure and tachycardia in 1975, Waagstein et al. provided the following explanation for the observed clinical improvement: "... reduction of a higher heart rate might reduce the energy demand of the myocardium and allow better diastolic filling and thus increase the stroke volume, thereby improving the efficiency of the heart and possibly allowing more energy to be used for contractile

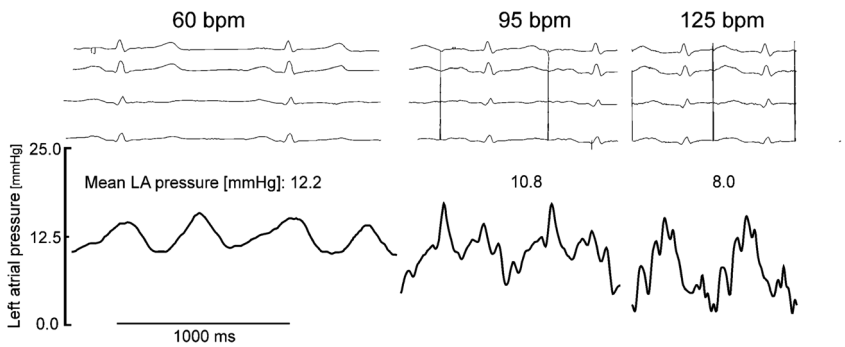

Fig. 1 Heart rated-induced change of left atrial pressure. Sequential left atrial pressure tracings and ECGs in a resting patient with a preserved ejection fraction with and without right atrial pacing (no pacing, 95 bpm, 125 bpm). Higher heart rates are associated with lower left atrial pressures

work" [28]. In a study published in 1979, Swedberg et al. proposed the following mechanism: "… When ß receptors are sensitized to catecholamines, any factor that raises catecholamine concentrations further may produce an abnormal cellular metabolic response and deterioration of mechanical performance" [29].

When the concept of ß-receptor blockade as a treatment for HFrEF came into its own in the 1990s, Waagstein and colleagues provided a more contemporary explanation for the benefit of ßbs. "…. The favorable effects of β-blockade in our study are consistent with the general hypothesis that excessive neuroendocrine activation may be detrimental" [30]. This suggested that HR reduction was not central to the favorable effects of ßbs, although many clinicians continued to believe that effects on HR were more than just a surrogate for neuroendocrine activation. The latter view was corroborated by meta-analyses that suggested a strong relationship between the degree of HR reduction and outcomes [31, 32]. Despite this, the prevailing view at this point favored neurohumoral blockade and not HR lowering as the principle therapeutic mechanism.

A setback to the neurohumoral paradigm came from the SHIFT heart failure trial in 2010 when a selective HR reduction of about 10 bpm with ivabradine provided a further reduction in mortality in HFrEF patients with insufficient HR control despite ßB therapy [33]. The authors of this trial astutely concluded: "our results support the importance of heart-rate reduction with ivabradine for improvement of clinical outcomes in heart failure and confirm the important role of heart rate in the pathophysiology of this disorder." Adding to this, the echocardiographic sub-study of the SHIFT trial directly confirmed that HR lowering resulted in a reduction in left ventricular chamber dimensions [34].

As discussed above, opinions about the benefits of lowering HR with ßBs have changed over time. Basic research has not provided any substantive insights into the underlying molecular mechanisms whereby HR lowering may improve outcomes in HFrEF. Nonetheless, it can now be argued that the ivabradine findings have reestablished HR lowering as an important mechanism that substantially explains the efficacy of ßBs. This view is also supported by several meta-analyses that demonstrated that the degree of HR lowering is more important than the dose of the ßB [31, 32, 35]. Together, these findings suggest that the concept of HR lowering has come full circle.

Heart rate lowering in heart failure with preserved ejection fraction—inadequate evidence

There are no large randomized controlled trials to evaluate HR lowering with ßBs or ivabradine in heart failure with preserved ejection fraction (HFpEF), as defined by the current diagnostic requirement of an ejection fraction above 50% [27]. The 2013 guideline committee states:"... to date, efficacious therapies have not been identified." However, in their treatment recommendations, the committee assigned a Class IIa recommendation for the use of ßbs: "…The use of beta-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HFpEF. (Level of Evidence: C)." Interestingly, the committee goes on to argue that "…slowing the heart rate is useful in tachycardia but not in normal resting heart rate; a slow heart rate prolongs diastasis and worsens chronotropic incompetence" [27]. This statement reveals another well-established negative effect of HR lowering medications: a reduced ability to increase the HR with exercise, which has a limiting effect on exercise capacity [36].

The only randomized trials that tested ßbs in HFpEF were SENIORS and J-DHF [37, 38]. The 2005 SENIORS trial compared nebivolol with placebo in patients with HFpEF, defined as an EF > 35%, and HFrEF, defined as an EF ≤ 35% [37]. The composite of all-cause mortality or hospitalization for cardiovascular causes was not improved by nebivolol and not different between the HFpEF and HFrEF groups. In J-DHF, a small randomized trial of carvedilol, the investigators performed a pre-specified analysis of patients with EF > 50% [38]. In 102 patients, carvedilol did not change any of the outcomes over 2 years.

In a retrospective analysis of the OPTIMIZE-HF registry that compared use versus non-use of ßBs on the composite endpoint of all-cause mortality or HF rehospitalization in 1099 pairs of HFpEF propensity-matched patients (here, HFpEF was defined as an EF ≥ 40%), the ßB group did not demonstrate a reduction of the composite endpoint over 6 years of follow-up [39].

In a recent trial that studied up-titration of bisoprolol or carvedilol over 12 weeks in HFpEF and HFrEF patients, the authors reported that NT-proBNP remained stable in HFrEF patients but increased significantly in HFpEF patients [40]. The functional effects of selective HR lowering with ivabradine in patients with HFpEF (EF > 50%) were evaluated in two studies reported in 2013 and 2015[36, 41] These studies were contradictory. The first [41] found an improvement in functional capacity while the second [36] demonstrated a reduction in exercise capacity. In summary, at present, there is no convincing evidence to support pharmacological HR lowering in HFpEF.

Heart rate lowering in coronary artery disease and a preserved ejection fraction—more harm than benefit

The effects of ßB treatment on long-term outcomes in patients with stable coronary artery disease have not been thoroughly

evaluated in the era of modern reperfusion therapies. A recent prospective, observational cohort study of about 180,000 patients after acute myocardial infarction without heart failure did not demonstrate a benefit of ßBs despite including patients with ejection fractions as low as 30% [42]. SIGNIFY is another recent trial that provided a direct insight into the effect of selective HR lowering with ivabradine in about 19,000 randomized patients with coronary artery disease and a HR greater than 70 bpm [43]. Patients with HF and/or an EF ≤ 40% were excluded, and the average EF was 56%. Over a medium follow-up of just over 2 years, there were no significant beneficial effects of an average 10 bpm HR-lowering with ivabradine versus placebo. The outcome that came closest to significance was a 20% *increase* in hospital admissions for heart failure ($p = 0.07$) in patients randomized to ivabradine. Analysis of adverse outcomes demonstrated that HR lowering by ivabradine increased the risk for atrial fibrillation by about 40% ($p < 0.001$). This large randomized study was the first to directly demonstrate a detrimental effect of selective HR lowering in patients with coronary artery disease and a normal or preserved EF. In addition, a meta-analysis of acute coronary syndrome trials that compared effects of ßBs for up to 1 year in the pre-reperfusion and reperfusion era also concluded that ßBs increased the risk of HF in the post-reperfusion era by more than 10% [44]. These findings support the view that HR lowering in coronary artery disease patients with normal ejection fraction results in adverse outcomes, such as heart failure and atrial fibrillation, that are typically associated with longstanding diastolic dysfunction [43, 44]. Nonetheless, it is important to keep in mind that ßBs are effective antianginal drugs and should not ordinarily be withheld from patients with symptoms of demand ischemia.

In the following section, we will attempt to integrate the available clinical and experimental data on HR manipulations to better understand the contradictory results of HR lowering in different patient groups.

Hemodynamic and structural effects of lower heart rates—reconciliation of conflicting data

The cardiovascular effects of HR lowering can be broken down into hemodynamic effects and structural effects on the myocardium.

Hemodynamic effect of HR lowering HR lowering, regardless of the mechanism, prolongs the filling of the cardiac chambers, which increases filling pressures and LV diastolic wall stress [20, 45, 46]. This normal effect of HR lowering mimics the effects of diastolic dysfunction on LV filling pressure and increases the risk of atrial fibrillation and heart failure as was evident in SIGNIFY and coronary artery disease ßB trials [43, 44]. It also explains why BNP levels are higher in patients who receive HR lowering medications [21, 22, 40]. Predictably, lower HRs also result in larger stroke volumes and higher central blood pressures, which can induce LV hypertrophy, a common substrate for atrial fibrillation and HFpEF [19, 20, 47, 48]. Higher central blood pressures may also directly contribute toward an increased risk for stroke and cardiovascular death as reported in patients receiving atenolol for the treatment of hypertension in LIFE [13]. Clearly, these mechanisms are less important in HFrEF where HR lowering improves cardiac function and cardiovascular outcomes over time.

Effect of HR on LV structure A superimposed effect of lower HRs is mediated by an innate myocardial remodeling process that results in LV size changes [49]. It is well-established that a sustained *increase* in HR can induce eccentric LV remodeling in both animal models and patients [50–54]. This process plays a role in many physiological adaptations, e.g., pregnancy and extreme endurance sports, but is clinically most prominent in a form of pathological remodeling commonly known as tachycardia-induced dilated cardiomyopathy [49–52]. Importantly, simple HR lowering is sufficient to revert the enlarged LV to a normal size and EF [27, 50–54]. It can therefore be argued that, in the case of a dilated LV chamber, HR lowering leads to reverse, *concentric* remodeling that results in LV size reduction which is a component of the observed benefits in dilated cardiomyopathy and HFrEF. In subjects with a normal LV size, this mechanism is offset by a larger effect of prolonged LV filling, which increases end-diastolic chamber dimensions, as demonstrated in the atenolol arm of the LIFE study [13, 55]. The hemodynamic and structural effects of HR are summarized in Table 1.

Effects of higher heart rates—challenging the paradigm

There are no medications that can selectively increase HR, but studying patients with atrial fibrillation provides some insights

Table 1 Left ventricular effects of heart rate changes

Left ventricle	Lower heart rates	Higher heart rates
Hemodynamics		
LV filling	↑	↓
LV pressures	↑	↓
Central systolic BP	↑	?
Central diastolic BP	↑	?
BNP levels	↑	?
Structural adaptation	Concentric	Eccentric
LV size	↓	↑

Hemodynamic and left ventricular (LV) structural effects of heart rate changes. BNP, brain natriuretic peptide, ↑ increased, ↓ decreased, ? unknown

into the effects of elevated HRs. The RACE-2 study was a thought-provoking and potentially revealing clinical trial that questioned the canonical thinking in regard to HR [56]. This guideline influencing trial compared two rate control strategies in patients with atrial fibrillation. The strict rate control group had a HR goal of less than 80 bpm. In the lenient rate control group, HRs of up to 110 bpm were allowed. This study established the non-inferiority of higher HRs with a numerical signal towards better outcomes. Although the findings of the RACE-2 study cannot be generalized to patient populations in sinus rhythm, the results may provide a first clue that higher HRs are not always detrimental.

Summary

There is unequivocal evidence that pharmacological heart rate lowering is beneficial in patients with heart failure and a reduced ejection fraction. In patients with a normal ejection fraction, pharmacological heart rate lowering can be associated with adverse cardiovascular outcomes. This was documented in patients with uncomplicated hypertension treated with ßBs and in patients with stable coronary artery disease treated with ivabradine. Recent analyses suggest that post-myocardial infarction patients without heart failure also do not benefit from the use of beta-blockers.

Based on these results, it appears that we have incorrectly extrapolated epidemiological findings and offer seemingly sensible physiological explanations that lead us to expect beneficial outcomes from medications that lower the heart rate. This widespread but incorrect assumption may explain why beta-blockers are prescribed to about 11% of the adult US population but only about 1%, namely patients with heart failure and reduced ejection fraction, are provided a survival benefit [17, 18, 27].

The growing evidence of adverse outcomes with HR lowering medications in diverse patient populations with a normal or preserved ejection fraction call for a serious reassessment of the effects of heart rate manipulations in clinical trials. There also remains much to be learned from connecting clinical observations, population-based data, and putative mechanisms.

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