The role of heart rate and ivabradine in acute heart failure

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Abstract

Resting heart rate (HR) is considered a powerful predictor of mortality both in healthy subjects and in cardiovascular (CV) patients, including those affected by heart failure (HF). Its reduction below 70 bpm is the treatment target in chronic HF with reduced ejection fraction (HFrEF) when sinus rhythm is present. In acute HF (AHF) HR is usually elevated but its role as risk marker is still unknown. Notably, in unstable patients, beta-blockers can be reduced or stopped, thus enhancing this phenomenon. Moreover, some data in literature suggest that HR reduction during hospitalization or HR at discharge or in the vulnerable phase after it are more predictive of early-term events and may be therapeutic targets. On the other hand, ivabradine is a pure HR-lowering drug with no effects on inotropism. Its role in the AHF setting has been recently investigated and is the object of this review.

Pharmacology of ivabradine and current indications

Ivabradine is the only pure heart-lowering drug on commerce [1]. It acts specifically blocking the I_f ("funny") current in the sinoatrial node [2], where myocytes have the unique ability to generate a spontaneous slow diastolic depolarization in order to provide a subsequent action potential. Ivabradine has a high selectivity for I_f channels [2] blocking them by entering their pore from the intracellular side in a concentration-dependent manner only when the channel is open [3,4]. It reduces the firing rate of the pacemaker cells in the sinoatrial node without affecting the duration of the action potential and without interfering with other ionic currents [3,5]. Consequently, ivabradine has no effects during atrial fibrillation (AF). Moreover, being I_f inhibition dependent from the frequency of channel opening, from the voltage and the sodium concentration, ivabradine is more effective at a higher HR [4].

In the SHIFT (Systolic Heart failure treatment with the I(f) inhibitor ivabradine Trial) 6505 outpatients affected by chronic heart failure (HF) with left ventricular (LV) ejection fraction (EF) ≤35% and HR ≥70 bpm in sinus rhythm (SR) were randomized to ivabradine (target dose 7.5 mg bid) or placebo on top of standard medical therapy [6]. Ivabradine reduced by 18% the primary composite endpoint of cardiovascular (CV) death or worsening HF, mainly acting on HF rehospitalisation and HF death. In a subsequent analysis of the SHIFT trial regarding the subgroup with HR ≥75 bpm all-cause mortality and CV mortality were both decreased by 17%, suggesting that the higher the resting HR the more beneficial the effect of the drug [7]. Similar analyses in the pooled population from the SHIFT and the BEAUTIFUL trials confirmed the same findings [8].

In the setting of HF, beta-blockers are one of the first line therapy (recommendation class IA) and reduce mortality and morbidity but have not been tested in congest or decompensated patients. Beta-blockers should be initiated in clinically stable patients at a low dose and gradually up-titrated to the maximum tolerated dose. In patients admitted due to acute HF (AHF) beta-blockers should be cautiously initiated in hospital, once the patient is stabilized [9] and the dose might be halved if worsening sign and symptoms of HF to facilitate recovery [10]. According to the results of the SHIFT and the BEAUTIFUL trials, in the recent European Society of Cardiology (ESC) guidelines ivabradine has a class of recommendation IIa to reduce CV mortality and HF hospitalization in symptomatic patients with LVEF ≤35% and resting HR ≥70 bpm in SR despite the maximum tolerated dose of beta-blocker, ACE inhibitor (or angiotensin receptor blocker) and mineralocorticoid receptor antagonist (or angiotensin receptor blocker) (level of evidence B) or in those not tolerating or having contraindications to beta-blocker, already receiving ACE inhibitor (or angiotensin receptor blocker) and mineralocorticoid receptor antagonist (or angiotensin receptor blocker) (level of evidence C) [9].

Heart rate in chronic heart failure: brief overview

With blood pressure, HR is a major clinical sign in the evaluation of CV patients. Albeit being simple and immediate, HR

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uncovers most information about the hemodynamic status of the patient, particularly if affected by HF. From this point of view, HR can be seen as a biological marker of LV deterioration, thus predicting a higher incidence of events and representing an important therapeutic target.

Resting HR, particularly nocturnal, is considered a powerful predictor of mortality in healthy subjects [11,12]. Indeed, the Framingham study showed a 14% increase in the all-cause mortality for every 10 bpm increment in the basal HR and an increased risk of developing HF in people with HR >80 bpm [13]. Moreover, every 1-bpm in resting HR accounted for a 4% increase in the risk of developing LV dysfunction and HF in the asymptomatic participants of the MESA (Multi-Ethnic Study of Atherosclerosis) [14].

HR has a prognostic role in chronic HF patients with LV dysfunction in a non-linear manner [15,16]. Over 70 bpm, an increment in resting HR of 1 and 5 bpm has been linked to a higher cumulative risk of death for CV causes and to a higher rate of hospitalizations for HF, of 3 and 16% respectively [15]. In the control group of the SHIFT patients with the highest HR (≥ 87 bpm) were at more than 2-fold higher risk for the primary composite endpoint than were patients with the lowest HR (70-71 bpm) [15].

The optimization of medical therapy in real world HF patients is unsatisfactory due to the high complexity of such patients (*e.g.*, comorbidities) with respect to those enrolled in randomized clinical trials [6,17-20]. In this context ivabradine is a powerful tool to better control HR and reduce mortality [21]. It seems that about 12% of HF outpatients need treatment with ivabradine after medical therapy optimization [22,23]. Interestingly, in a sub-analysis of the SHIFT, the benefit of ivabradine was maintained also in non-adherent or becoming non-adherent patients during the trial, suggesting that also reducing the HR for a short period might provide prolonged beneficial effects [24].

Heart rate and ivabradine during hospitalization for acute heart failure

The role of HR as a new therapeutic target is emerging in the context of AHF. European and Italian registries showed that patients admitted with AHF have higher basal HR as compared to patients with chronic HF [25,26]. However, Literature is still controversial regarding the prognostic significance of basal HR in patients hospitalized for AHF. For example, in the PROTECT (Adenosine A1 Receptor Antagonist Rolofylline in Patients with Acute Heart Failure and Renal Impairment) study, basal HR was shown to be part of model designed to predict the occurrence of adverse events at 7 days [27]. Bertomeu-Gonzalez *et al*. observed that at admission high HR was predictive of worse prognosis in patients with AF, but not in those with SR [28]. A J-shaped relationship between HR at admission and in-hospital mortality was found by Bui *et al*., with 70-75 bpm as the HR range with the lowest risk [29]. They also observed that an early HR reduction during the first days of hospital stay is predictive of better prognosis. However, when long-term events were considered, HR at admission was shown to lose its predictive value [18,26]. This could be explained by the fact that HR at admission is a hallmark of hemodynamic status and neurohormonal storm, both improving in parallel with decongestion. In the Acute HEArt Failure Database (AHEAD) Main registry, authors compared patients admitted for AHF by the presence of hypertensive HF, acute pulmonary oedema, cardiogenic shock, high output HF and right ventricular HF, observing a mean HR of 132 bpm in high output HF, whereas HR ranged from 90 to 98 bpm in the other situations. At discharge, HR >80 bpm was a significant predictor of early mortality with HR 1.33 [30].

Moreover, a higher HR is related to sympathetic overactivity, greater oxygen consumption and lower myocardial coronary perfusion time [31], as well as increased shear stress with inflammatory endothelial response [32]. Of note, as shown regarding natriuretic peptides, the magnitude of the initial neurohormonal activation is not related to the patient's conditions at the time of discharge [33], but the variation during hospitalization and the value at discharge are much more related to long-term prognosis [33-35]. The same, a reduction in HR during hospital stay was shown to be protective against the development of long-term events, independently of the target achieved [36], as well as early post-discharge HR does [37,38]. Therefore, clinical stabilization until discharge of patients admitted for AHF is a crucial period in which HR control should be pursued. Real world data, as in chronic HF setting, show that HR <70 bpm is achieved in less than 50% at discharge [39], with beta-blockers at target dose only in 25% of patients [25]. However, it must be noted that some studies demonstrated that the benefit associated with beta-blockers is mainly related to the achievement of HR control than the recommended dose of beta-blockers [40,41].

In AHF a higher HR is both a compensatory mechanism against hypotension and a contributor to worsening HF, so that indication of lowering HR drugs is not clear. Lourenco et al. demonstrated that a higher admission heart rate predicted survival advantage in acute HF. Patients with heart rate ≥100 bpm had a multivariate-adjusted HR of 12-month death of 0.57 (95%CI: 0.39-0.81), and the HR was 0.92 (0.85-0.98) per 10 bpm increase in heart rate. Patients presenting with tachycardia and discharged with a controlled heart rate had better outcome than those admitted non-tachycardic or discharged with a non-controlled heart rate (death rate was 14.9% and 37.7%, respectively). Association of heart rate with mortality was stronger in patients in SR and in those with systolic dysfunction [42]. In a small cohort of AHF patients not needing inotropes ivabradine safely reduced HR improving New York Heart Association (NYHA) functional class and natriuretic peptides level [43]. The same was retrospectively found by Pascual Izco *et al.* [44]. Furthermore, the ETHIC-AHF trial randomized 71 AHF patients with LVEF <40% and SR with HR >70 bpm to receive ivabradine and beta-blockers vs beta-blockers alone 24 hours after hospital admission. HR at one and 4 months after discharge were significantly lower in the first group, and significant differences were found with respect to LVEF and natriuretic peptides levels, but the trial did not found differences in clinical events (re-hospitalization/death) at 4 months [45]. In addition, ivabradine, as a pure HR-lowering drug without negative effects on inotropism, can be useful to counteract inotrope-induced sinus tachycardia which often prevent patient's stabilization [44,46,47] and does not have the limitations of beta-blockers and non-dehydropiridine calcium channel blockers. Cavusoglu *et al*. ran an ECG Holter monitoring in 58 AHF patients since the beginning of dobutamine therapy, half of them treated with ivabradine. They found that in the control group, mean HR gradually and significantly increased at each step of dobutamine infusion whereas no significant increase in HR was observed in the ivabradine group [48].

Recently, Colucci *et al*. suggested that for patients who are already taking ivabradine, management depends upon the severity of HF decompensation, heart rate and hemodynamic instability. If an increased heart rate appears necessary to maintain cardiac output, then may be considered holding ivabradine in patients with severe decompensation [49]. Contrarily, this agent should not be initiated at the time of presentation with an episode of ADHF. Based on the

above-mentioned studies, during hospitalization ivabradine can be added on top of beta-blocker therapy to improve HR control if the latter are poorly tolerated or contraindicated. Unfortunately, no studies are available on the timing need for reaching the HR target <70/m. Safety and efficacy of this drug must be confirmed by focused clinical trials.

In the setting of acute peripartum cardiomyopathy a retrospective study from a German national registry found that those patients treated with ivabradine soon after diagnosis had a better prognosis compared with that reported so far in registries from Germany, United Kingdom and South Africa [50].

It is also important considerer that AF is the most frequent arrhythmia in patients with HF irrespective of LV ejection fraction, can impair LV function leading to worsening symptoms and can also be a precipitant cause in AHF [9], ranging from 5% in mild to 10-26% in moderate and up to 50% in severe HFrEF [51,52]. It was observed in a 1-year follow-up a prevalence of 44% in chronic HF ad of 38% in AHF [53]. In the setting of AF Ivabradine should not be administered because it has no effect on HR, as the atrial rhythm derives from a chaotic electrical activation and is not liked to I_f ionic current. Moreover, in patients at risk of developing AF, the drug is not indicated because it increases the risk of AF itself. In a metanalysis, ivabradine treatment was associated with a relative risk of AF of 1.15 (95% CI 1.07 to 1.24, p=0.0027) among 21 571 patients considered, estimating that the number needed to harm for ivabradine would be 208 (95% CI 122 to 667) per year of treatment [54]. This can represent an important limitation of the use of ivabradine in the clinical practice, reducing the potential number of patients that could benefit of the HR reduction induced.

The setting of cardiogenic shock: few evidences

Trials in cardiogenic shock are always difficult since the complexity of such patients. Few cases report about ivabradine use in this setting: one related with tachycardiomyopathy after heart transplantation [55], one with idiopathic cardiomyopathy [56] and some with acute myocardial infarction, also by our group [57,58]. Barillà *et al*. ran a pilot trial about ivabradine administration in patients with cardiogenic shock complicating ST-elevation myocardial infarction, founding that it can be effectively administered by nasogastric intubation and it is associated with a short-term favorable outcome in term of better recovery of LVEF [59]. In 2011 the MODI(f)Y trial has been presented as a prospective single center open label randomized controlled phase II trial to evaluate the effect of ivabradine in patients with multi-organ dysfunction syndrome, but results have not been published yet [60].

Heart rate and ivabradine in the early post-discharge phase

The vulnerable phase after AHF corresponds to the first 90 days after discharge, when re-hospitalizations are frequent and related to failure of achieving medical therapy optimization during the hospital stay, inadequate home care assistance or compliance to medical therapy and advanced status of the disease [61]. Such early re-hospitalizations are related to CV causes or other comorbidities and account up to 25% out of discharges after AHF [37,62,63]. As mentioned above, HR in the early post-discharge phase has a prognostic significance [37,38]. A *post-hoc* analysis of the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan) trial revealed that in the early pre-discharge increases of HR >70 bpm were independent predictors of mortality during the early follow-up in patients with SR and LV dysfunction who had been admitted for AHF and previous chronic HF [18]. Moreover, every 5-bpm increment in HR in the first week and at four weeks post-discharge were independently associated with a 13% and 12 % increased of overall mortality at a median follow-up of 10 months, respectively [18]. The EFFECT-HF (Enhanced Feedback for Effective Cardiac Treatment) program enrolled 9000 HF patients after discharge from a phase of clinical deterioration. In this context, Habal *et al*. found a significant correlation between HR and early mortality, particularly if HR was >80 bpm [64]. The AHA GWTG-HF (American Heart Association Get with the Guidelines Program) prospective registry included 46,000 patients with the same characteristics and highlighted a correlation between HR at discharge and the likelihood of re-hospitalization for all-causes, both in patients in SR and in AF [65]. In addition, a sub-analysis of this registry performed on more than 39000 patients admitted for AHF with or without LV systolic dysfunction included HR as in-hospital independent prognostic factor, together with age, HF as the cause of hospital admission, systolic blood pressure at admission, plasma sodium concentration, serum creatinine levels, and LVEF <40% [66]. Other similar good prognostic scores, however, did not include HR [67-69]. A post-hoc analysis of the SHIFT evaluating the impact of chronic exposure to ivabradine on early readmissions during the vulnerable period showed that ivabradine was associated with 20-30% less all-cause hospitalizations at 1 month, 2 months and 3 months [70]. In the INTENSIFY study a group of 1,956 HFrEF patients with an initial SR (85 ± 11 bpm) were treated with ivabradine, in 77.8% in addition to a beta-blocker and after 4 months of treatment, heart rate has fallen down to 67 ± 8.9 bpm. In parallel with this heart rate reduction, the proportion of patients with signs of decompensation fell from 22.7% initially to 5.4%, and the proportion of BNP levels > 400 pg/mL dropped from 53.9% to 26.7%. This coincided with a reduction in NYHA class from 9.6% (I), 51.1% (II), 37.2% (III) and 2.1% (IV) initially to 24.0% (I), 60.5% (II), 14.8% (III) and 0.7% (IV), respectively [71]. It is therefore reasonable to consider post-discharge HR as an important contributor in the prognostic stratifications of patients with a recent clinical decompensation of chronic HF.

Conclusions

In AHF patients HR during hospitalization, at discharge and early after discharge are associated with early-term events and can be a therapeutic target [36-48] and possible pros and cons of the use of ivabradine are summarized in Table 1. Ivabradine is approved in the setting of chronic HFrEF [9]. However, its pharmacological properties make the drug potentially useful also in the setting of AHF, where mortality and early re-hospitalization are still an important healthcare burden. The findings reported suggest that in-hospital or early post-discharge initiation of ivabradine could be useful to improve early outcomes in patients hospitalized for AHF [70], even if proper clinical trials are still needed. The usefulness of ivabradine, compared with beta-blocker up-titration, with the addition of digoxin, or just with maintenance of ongoing therapy, is still unknown [72]. Certainly, ivabradine lets HR decrease without affecting inotropism and can counteract inotrope-induced

Table 1. Heart rate and ivabradine in acute heart failure.

Time	Meaning of high heart rate	Pros of ivabradine	Cons of ivabradine
Admission for acute heart failure and first days of hospitalization	Marker of hemodynamic instability and neurohormonal storm (unproved prognostic role)	Prevents tachycardia-induced myocardial ischemia when beta-blockers cannot be uptitrated or administered (*e.g.*, reduced coronary perfusion in diastole, increased oxygen consumption, plaque rupture/ endothelial dysfunction, reduced contractility, increased afterload) Counteraction to inotrope-induced tachycardia	May hinder the physiological hemodynamic adaptation mechanism induced by HR increment (*e.g.*, maintain adequate blood pressure)
End of hospitalization and vulnerable phase post-discharge	Suboptimal therapy optimization (independent prognosticator of early-term outcomes)	Favors HR <70 bpm reducing events Prevents LV remodeling	Increased risk of AF in patient already at risk of AF itself Side effects (*e.g.*, symptomatic and asymptomatic bradycardia and conduction disturbances, phosphenes, blurred vision)

AF, atrial fibrillation; HF, heart failure; HR, heart rate; LV, left ventricular.

tachycardia in more compromised patients [46-48]. HR is easy and costless to monitor and, together with congestion, represents a major player in the outcomes of AHF patients [73]. Ivabradine is promising in AHF setting and needs further dedicated clinical trials to extend its indications in such patients.

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