International Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Heart rate as a prognostic marker and therapeutic target in acute and chronic heart failure

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ARTICLE INFO

Article history:
Received 16 January 2017
Received in revised form 12 June 2017
Accepted 22 September 2017
Available online xxxx

Keywords:
Acute heart failure
Heart rate
Ivabradine
Beta-blockers
Sinus rhythm
Atrial fibrillation

ABSTRACT

Since increased heart rate (HR) is associated with higher mortality in several cardiac disorders, HR is considered not only a physiological indicator but also a prognostic and biological marker. In heart failure (HF), it represents a therapeutic target in chronic phase. The use or up-titration of beta-blockers, a milestone in HF with reduced left ventricular ejection fraction (LVEF) treatment, is at times limited by patients' hemodynamic profile or intolerance. Ivabradine, a HR-lowering drug inhibiting the f-current in pacemaker cells, has been shown to improve outcome in patients with chronic HF, in sinus rhythm with increased HR beyond beta-blocker therapy. The rationale for this review is to update the role of HR as a prognostic biomarker and a potential therapeutic target in other scenarios than chronic HF; namely, in patients with coexisting atrial fibrillation (AF), in HF with preserved LVEF (HFpEF), in acute HF, and in patients discharged after an episode of acute HF. Preliminary studies and case reports that evaluated the use of ivabradine in the setting of acute HF will be summarized. Recent results of HR reduction in the setting of HFpEF with ivabradine will be presented. Finally, data from large registries and trials that evaluated the prognostic impact of HR in patients with acute HF and sinus rhythm or AF will be reviewed, showing that only patients in sinus rhythm may benefit from HR reduction.

1. Introduction

The prevalence of heart failure (HF) in the general population is around 2% and it shows an exponential growth as age increases. The natural history of the disease is characterized by acute exacerbation phases alternated with periods of clinical quiescence, with a progressive decline in terms of functional capacity and quality of life. Studies have reported a mortality rate of 5 to 7% during hospitalization, and 20 to 25% at 1 year after an episode of acute HF; while the mortality rate among patients with chronic HF has been reported of 6% at 1 year since diagnosis [1,2]. The observed 1-year hospitalization rates were about 30% in acute HF and 23% in chronic HF [2], although significant regional variations have been observed reflecting differences in the characteristics and/or management of these patients [1,3]. In HF several markers have been shown effective in the determination of diagnosis and prognosis of the disease; moreover, they represent valuable indices of disease severity and response to treatment [4,5]. Among them, resting HR represents a physical easily measurable sign with prognostic impact that can be also used as therapeutic target in the setting of chronic HF with reduced ejection fraction (HFrEF) [6]. It must be noted that reproducibility of HR can be affected by the setting in which HR is taken (Holter HR, office HR, HR taken in the ECG, HR measured after 10 min of rest). Nevertheless, the SHIFT Holter substudy found that the mean office HR was only 3 beat per minute (bpm) higher compared with mean 24-hour HR based on Holter recording [7]. The rationale for this review is to update the role of HR as a prognostic biomarker and a potential therapeutic target in other scenarios than chronic HF; namely, in patients with coexisting atrial fibrillation (AF), in HF with preserved LVEF (HFpEF), in acute HF, and in patients discharged after an episode of acute HF.

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https://doi.org/10.1016/j.ijcard.2017.09.191
0167-5273/

2. Pathophysiology of HR in sinus rhythm and AF

HR represents an important determinant of myocardial oxygen consumption and of coronary blood flow playing a central role in the adaptation of cardiac output to the metabolic requirements of the organism. In physiological terms, the measured HR is the final determinant of the regulation of the so-called *intrinsic* HR by the autonomic nervous system at the level of the sino-atrial node. It has been advocated that mean HR, and even more nocturnal HR, is associated to a higher mortality in several cardiac conditions [8]. The Framingham study has shown a 14% increase in the all-cause mortality for every 10 bpm increment in the basal HR. In the same study a basal HR >80 bpm was also associated to a significantly increased risk of developing HF [9]. In patients with left ventricular (LV) dysfunction and HF, HR > 70 bpm with an increment in resting HR of 1 and 5 bpm has been linked to a higher cumulative risk of death for cardiovascular causes and to a higher rate of hospitalizations for HF, of 3 and 16% respectively [10]. Moreover, in the multicentric CHARM trial, an increase in HR during follow up compared to the previous outpatient clinic visit was a significant predictor of events, thus confirming the importance of strictly monitoring HR over time both in the setting of outpatient clinic visits and with remote monitoring techniques [11]. HR can therefore be identified as a biological marker of LV deterioration and higher incidence of events and could represent an important therapeutic target. Such aim can be achieved both with beta-blockers, calcium-channel blockers, digoxin, amiodarone, but also with medications such as ivabradine, which selectively targets HR in subject in sinus rhythm (SR) with no other cardiac effects and only minimal consequences on other organs [6,12]. This relation between increased HR and increased cardiovascular events is apparently lost in patients with AF [13,14], who are already at increased risk compared to patients in SR [15,16]. Furthermore, even if severity of symptoms (mainly dyspnea) in patients with permanent AF is associated with cardiovascular outcome, it does not seem associated with increased HR [17]. Similarly, HR does not influence quality of life in patients with permanent AF [18].

2.1. Role of HR in chronic HF outpatients in SR and AF

In Table 1 are summarized the studies that explored the prognostic impact of HR in patients with chronic HF, where clearly emerged that increased HR was associated to mortality and adverse events in patients in SR [19–22]. In the SHIFT trial, where patients in SR ≥ 70 bpm with LVEF ≤ 35% were enrolled, it has been observed that in the control group, patients with the highest HR (≥87 bpm) were at >2-fold higher risk for the primary composite endpoint than were patients with the lowest HRs (70–71 bpm, hazard ratio 2.34, 95% confidence interval [CI] 1.84–2.98) [10]. This result was confirmed and extended in a subanalysis of the CHARM population [21], showing that resting HR is an independent predictor of outcome in patients with stable chronic HF without AF, regardless of LVEF or beta-blocker use. They also found that among patients in AF at baseline, HR had no predictive value [21].

Table 1
Studies that evaluate the prognostic role of heart rate in chronic heart failure (CHF) with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF) with and without atrial fibrillation (AF).

Author and year	Study/registry name	Main field	Number of patients	Main result concerning HR
Böhm et al. [10] 2010	SHIFT study	CHF, in SR ≥ 70 bpm, and LVEF ≤ 35%	3.264 patients (placebo group) and 3.241 patients (ivabradine group)	Risk of primary composite endpoint events increased by 3% with every beat increase from baseline HR and 16% for every 5-bpm increase
Castagno et al. [21] 2012	CHARM trial	CHF, comparison between subgroups with LVEF ≤40% and >40% and with or without AF	7599 patients	Patients in the highest HR tertile had worse outcomes when compared with those in the lowest heart rate group (e.g., for the composite of CV death or HF hospital stay hazard ratio: 1.23, 95% CI: 1.11 to 1.36, $p < 0.001$). The relationship between HR and outcomes was similar across LVEF categories and was not influenced by beta-blocker use. However, among patients in AF at baseline, HR had no predictive value.
Vazir et al. [11] 2015	CHARM trial	CHF	7.599 patients	An increase in HR from preceding visit was associated with a higher risk of all-cause mortality and the composite endpoint of CV death or hospitalization for HF (adjusted hazard ratio 1.06, 95% CI: 1.05–1.08, $P < 0.001$, per 5 bpm. Higher HR)
Cullington et al. [19] 2014	Single-centre prospective study	CHF and LVEF ≤ 50% with (24%) or without AF	2039 patients	No association between HR and survival in patients with AF at baseline and after therapy optimization at 1 year. For patients with SR, higher HR was associated with worse survival at baseline (hazard ratio 1.10) and after therapy optimization (1.13)
Simpson et al. [20] 2015	MAGGIC registry	CHF (HFrEF and HFpEF) with and without AF	3259 patients	An increased HR in patients with CHF and coexisting AF was not independently associated with 3-year mortality both in HFrEF and HFpEF. Higher HR in patients in SR was significantly associated with 3-year mortality
Li et al. [34] 2015	Swedish Heart Failure registry	CHF (HFrEF) with or without AF	11,466 patients with SR, 7392 patients with AF	Compared with HR ≤ 60 bpm, the adjusted hazard ration for all-cause mortality increased in SR for HR above 60 bpm and gradually increased with HR increment. Whereas in patients with AF the hazard ratio was significant only for HR > 100 bpm compared with HR ≤ 60 bpm.
Kapoor and Heidenreich [44] 2010	Stanford University Cardiology Division's registry	HFpEF (LVEF > 50%)	685 patients	After adjustment the hazard ratios for total mortality (relative to a HR of <60) were 1.26 (95% CI, 0.88–1.80) for HR 60–69, 1.47 (95% CI, 1.02–2.07) for HR 70–90, and 2.00 (95% CI, 1.31–3.04) for HR > 90 ($P = 0.01$ across all groups).
Böhm et al. [22] 2014	I-Preserve trial	HFpEF (LVEF > 45% and age > 60 years) with and without AF	3.271 patients in SR and 696 patients with AF	Each standard deviation (12.4 bpm) increase in HR was associated with an increase in risk of 13% for CV death or HF hospitalization ($P = 0.002$). No relationship between HR and outcomes was observed for patients in AF

HR, heart rate; LVEF, left ventricular ejection function; bpm, beat per minute; SR, sinus rhythm; CV, cardiovascular; CI, confidential interval.

Please cite this article as: F. Oliva, et al., Heart rate as a prognostic marker and therapeutic target in acute and chronic heart failure, Int J Cardiol (2017), https://doi.org/10.1016/j.ijcard.2017.09.191