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Emerging role of ivabradine for rate control in atrial fibrillation

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***Abstract*:** Control of ventricular rate is recommended for patients with paroxysmal, persistent, or permanent atrial fibrillation (AF). Existing rate-control options, including beta-blockers, nondihydropyridine calcium channel blockers, and digoxin, are limited by adverse hemodynamic effects and their ability to attain target heart rate (HR). Ivabradine, a novel HR-controlling agent, decreases HR through deceleration of conduction through I_f ('funny') channels, and is approved for HR reduction in heart failure patients with ejection fraction less than 35% and elevated HR, despite optimal pharmacological treatment. Because I_f channels were thought to be expressed solely in sinoatrial (SA) nodal tissue, ivabradine was not investigated in heart failure patients with concomitant AF. Subsequent identification of hyperpolarization-activated cyclic nucleotide-gated cation channel 4 (HCN4), the primary gene responsible for I_f current expression throughout the myocardium, stimulated interest in the potential role of ivabradine for ventricular rate control in AF. Preclinical studies of ivabradine in animal models with induced AF demonstrated a reduction in HR, with no significant worsening of QT interval or mean arterial pressure. Preliminary human data suggest that ivabradine provides HR reduction without associated hemodynamic complications in patients with AF. Questions remain regarding efficacy, safety, optimal dosing, and length of therapy in these patients. Prospective, randomized studies are needed to determine if ivabradine has a role as a rate-control treatment in patients with AF.

Keywords: atrial fibrillation, funny channel, heart rate, ivabradine, rate control

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Introduction

Rate control to maintain a resting heart rate (HR) at less than 80 beats per minute (bpm) improves quality of life (QOL) and reduces morbidity in atrial fibrillation (AF). When compared with rhythm control, a rate-control strategy demonstrated reduced adverse drug effects, decreased hospitalizations, and no difference in mortality [Wyse *et al*. 2002]. The 2014 American College of Cardiology/American Heart Association (ACC/AHA) AF guidelines recommend ventricular rate control for patients with paroxysmal, persistent, or permanent AF. Traditional options for ventricular rate control include beta-blockers, nondihydropyridine calcium channel blockers (diltiazem, verapamil), and digoxin [January *et al*. 2014]. These agents prolong atrioventricular (AV) node refractoriness; however, their use is limited by adverse hemodynamic effects and their ability to attain target HRs.

Analysis of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, which compared rate- and rhythm-control strategies in AF, revealed that frequent medication changes and combination therapy are needed to attain target HR. Beta-blockers achieved target HRs in 70% of patients, while calcium channel blockers (54%) and digoxin (58%) were less effective [Olshansky *et al*. 2004]. Though adequate HR control was eventually achieved in over 80% of patients, typically through combination therapy, 15% required crossover to a rhythm-control strategy. Additionally, adverse events or other clinical findings led to drug discontinuation in 16.7% of the rate-control group [Wyse *et al*. 2002]. Beta-blockers and calcium channel blockers may cause adverse hemodynamic effects, including hypotension, bradycardia, high-degree AV block (heart block), and negative inotropic effects. Beta-blockers are also associated with

other adverse effects that may negatively impact QOL, such as bronchospasm and fatigue. Digoxin, a cardiac glycoside, reduces resting HR, but is ineffective in controlling ventricular rate response during exercise. While digoxin has positive inotropic effects, its use is typically reserved for AF patients who are refractory to first-line agents [January *et al.* 2014]. Recent studies evaluating digoxin in AF have associated its use with increased mortality [Turakhia *et al.* 2014; Washam *et al.* 2015]. Current alternative management strategies for AF patients who are unable to attain target HRs, or who are intolerant of rate-control agents, include AV node ablation with permanent pacemaker placement or conversion to a rhythm-control strategy [Swedberg *et al.* 2010]. Identification of a pharmacologic agent that provides reliable, predictable rate control with minimal adverse hemodynamic effects could have significant impact on AF management.

Ivabradine, a selective inhibitor of 'funny' current (I_f) in the sinoatrial (SA) node, is approved by the US Food and Drug Administration for reducing the risk of hospitalization for worsening heart failure (HF) in patients with stable, chronic HF with an ejection fraction (EF) of no more than 35%, who are in sinus rhythm with a resting HR $\geqslant$ 70 bpm and either on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use [Amgen Inc., 2015]. In the ivabradine and outcomes in chronic heart failure (SHIFT) study, ivabradine dosed to a maximum of 7.5 mg twice daily reduced HR by 8.1 bpm and resulted in a 5% reduction in hospitalization for worsening HF. Of note, pre-existing AF was an exclusion criterion, and patients in the ivabradine group were more likely to develop new-onset AF (ivabradine 9% *versus* placebo 8%; $p = 0.012$) [Swedberg *et al.* 2010]. Product labeling suggests that ivabradine be discontinued if AF develops [Amgen Inc., 2015].

As I_f currents were initially thought to be expressed exclusively in the SA node, patients with atrial arrhythmias were excluded from trials of ivabradine in chronic stable angina and HF. Recent experimental animal models have, however, identified hyperpolarization-activated cyclic nucleotide-gated cation channel 4 (HCN4), the primary gene responsible for I_f current expression throughout the myocardium [Herrmann *et al.* 2011; Ou *et al.* 2010]. The purpose of this article is to review the available evidence evaluating ivabradine for HR control in AF.

Preclinical studies

Data from animal models suggest a role of I_f channels in modulating conduction through the AV node [Verrier *et al.* 2014, 2015]. Verrier and colleagues investigated the effects of ivabradine on AV node conduction and its subsequent effects on ventricular rate in live porcine and guinea pig heart models with induced AF. Ivabradine 0.1 mg/kg was administered as an intravenous (IV) bolus over 5 minutes. HR reduction 60 minutes after ivabradine administration was statistically significant in the porcine model (117 $\pm$ 4.5 bpm to 84 $\pm$ 1.9 bpm; $p = 0.0001$), with no significant effect on mean arterial pressure (MAP). Ivabradine significantly increased both the P–R ($p = 0.0009$) and atrial-His (A–H; $p = 0.0008$) intervals in a rate-dependent manner. Ventricular rate during AF was decreased from 240 $\pm$ 21.4 bpm at baseline to 211 $\pm$ 24.6 bpm at 60 minutes ($p = 0.041$). Moreover, there was no difference in QT or MAP. The guinea pig heart model displayed similar rate-dependent effects without negative inotropic actions [Verrier *et al.* 2015].

The same researchers investigated the effects of ivabradine with concomitant ranolazine on AV node conduction. IV boluses of ranolazine (2.4 mg/kg followed by 0.135 mg/kg/minute continuous infusion) and ivabradine (0.25 mg/kg and 0.1 mg/kg) were administered to live porcine models. Ivabradine, alone, significantly decreased sinus rate from 111 $\pm$ 4 bpm to 90 $\pm$ 3.3 bpm ($p = 0.003$). The addition of ranolazine to ivabradine decreased sinus rate to 73 $\pm$ 2.9 bpm ($p = 0.002$), though this effect was not seen with ranolazine, alone. In the living porcine model, ivabradine, alone, and the combination of ivabradine and ranolazine significantly increased the P–R and A–H intervals, and increases were greater than the additive effects of either agent, alone. The ventricular rate was significantly decreased with the combination of ivabradine and ranolazine ($p < 0.01$), and this decrease was greater than ivabradine, alone ($p < 0.02$) [Verrier *et al.* 2014].

These porcine models demonstrated a significant rate-dependent slowing of AV node conduction and ventricular rate with ivabradine [Verrier *et al.* 2014, 2015]. The ivabradine doses of 0.1 mg/kg and 0.25 mg/kg used in these animal models have been studied in human subjects [De Ferrari *et al.* 2008; Manz *et al.* 2003; Verrier *et al.* 2015]. There were no significant effects on MAP in any study, which suggests that ivabradine reduces HR in AF without affecting hemodynamic parameters.

Furthermore, these results suggest that inhibition of I_f by ivabradine may enhance ventricular rate reduction in AF *via* decreased conduction through the AV node [Verrier *et al.* 2014, 2015].

Case reports

The first case report of ivabradine use in AF involved a 75-year-old female with ischemic HF (EF of 35%) receiving ivabradine 2.5 mg twice daily [Moubarak *et al.* 2014]. She was found to be in AF upon hospital admission, with no concurrent beta-blockers or digoxin for rate control. Upon retrospective discovery of ivabradine use in the setting of AF, the patient agreed to wear a 24-hour Holter monitor to confirm permanent AF. Ivabradine was discontinued, and a second 24-hour Holter monitor record was completed 7 days later for comparison, and the patient was still in AF. Average HR was compared on and off treatment, and observed values were 80.1 bpm and 87.6 bpm, respectively. No adverse effects were noted.

A second patient case of ivabradine use in AF involved a 59-year-old male with persistent AF (resting HR >100 bpm) [Kosiuk *et al.* 2015]. The patient was diagnosed with tachycardiomyopathy with an EF of 35%. The patient's previous medication history was not reported but it was noted that he had failed previous treatments for AF. Therefore, he was initiated on ivabradine 10 mg/day for rate control. Electrocardiogram (ECG) readings displayed a decrease in mean HR for the first 3 days of ivabradine therapy (mean 102 bpm decreased to 84 bpm). Comparison of treadmill stress tests prior to and post ivabradine displayed a decrease in the maximal HR (from 169 bpm to 153 bpm) without changes in arterial pressure (160/80–163/93 mmHg). Benefits were also seen on repeat echocardiography in which the EF improved to 50%. Adverse effects were not noted, and it is unknown if the patient was continued on therapy.

These patient cases suggest ivabradine may have a HR-lowering effect in permanent and persistent AF. The first patient case used an ivabradine dose of 2.5 mg twice daily, which is lower than the recommended starting HF dose of 5 mg twice daily [Amgen Inc., 2015]. Product labeling for ivabradine states that it should be used in those with a contraindication to beta-blockers; however, it is unknown if these patients had this contraindication [Amgen Inc., 2015]. Unfortunately, these patient cases are limited in their retrospective and observational nature and report HR responses from short-term follow up. More long-term, prospective data will be needed to evaluate the benefit of ivabradine for rate control in humans.

Open-label trial

In addition to anecdotal evidence of the potential benefit of ivabradine in AF, one open-label pilot study has been published. Guiseppe and colleagues enrolled six patients with persistent or permanent AF to evaluate the addition of ivabradine to beta-blockers on improvements of HR and clinical condition [Guiseppe *et al.* 2016]. Patients were included if they were on maximally tolerated beta-blocker dosages, with a resting HR greater than 110 bpm, and dyspnea with minimal exertion. Exclusion criteria were previous diagnoses of pre-excitation syndrome or recent hospitalization. Baseline testing included ECG monitoring, 6-minute walking test (6MWT) and perceived dyspnea *via* the Borg's scale score (6–20 with 20 considered maximal exertion). These tests were repeated after 30, 60, and 90 days of ivabradine therapy. All patients were initiated on ivabradine at a dose of 2.5 mg twice daily and titrated to a maximum dose of 7.5 mg twice daily if HR decreased by up to 10% from baseline in response to therapy. Subjects had a mean baseline HR of 109.1 bpm. At baseline, four patients were on carvedilol (mean dose 22.3 mg/day) and two were on bisoprolol (mean dose 5.5 mg/day). Mean HR decreased significantly from baseline with 90 days of treatment (mean dosage 10.8 mg/day). Reduction of HR ranged from 19.8% to 34.1%, and appeared to have a dose-dependent effect. Two subjects were considered poor responders with HR reductions of less than 10 bpm from baseline. Maximum HR was decreased across groups in a similar manner, and blood pressure remained unchanged from baseline. The 6MWT and the Borg's scale score were improved at 3 months in the four patients with HR response to ivabradine [Guiseppe *et al.* 2016]. These results suggest HR reduction benefits when ivabradine is added to beta-blockers in AF. The positive effect was observed without associated bradycardia or adverse events over 3 months [Guiseppe *et al.* 2016]. Mean doses of beta-blockers used in this trial were similar to those observed in previous clinical trials (carvedilol 25 mg/day and bisoprolol 6.2 mg/day) [Swedberg *et al.* 2010]. This study is limited by its small sample size, open-label design, and short study duration.

Discussion

Limited evidence exists for the use of ivabradine for HR control in patients with AF. Current literature is confined to case reports and one open-label trial. Mean doses of ivabradine administered in the open-label trial (10.8 mg/day) were lower than those used in clinical trials for HF, although escalating doses did appear to produce a dose-dependent effect on HR reduction [Guiseppe *et al*. 2016]. The average dose of ivabradine after 1 year in the SHIFT trial was 6.4 mg [standard deviation (SD) 1.6] twice daily with 70% of patients receiving the target dose of 7.5 mg twice daily. The net reduction in HR at 28 days after ivabradine initiation was 10.9 bpm [95% confidence interval (CI) 10.4–11.4], and by study end, the difference was 8.1 bpm (95% CI 7.5–8.7) [Swedberg *et al*. 2010]. Further evaluation of ivabradine for AF rate control will determine the optimal dose for this population.

There were no reports of adverse events associated with the use of ivabradine in the patient cases and open-label trial, however, the small sample sizes and short durations of therapy limit conclusions on safety [Guiseppe *et al*. 2016; Kosiuk *et al*. 2015; Moubarak *et al*. 2014]. In the SHIFT trial, significantly fewer serious adverse events occurred in patients taking ivabradine (45%) *versus* placebo (48%; $p = 0.025$), yet, rates of symptomatic and asymptomatic bradycardia, phosphenes (visual side effects), blurred vision and AF were significantly higher in the ivabradine group *versus* placebo. Overall rates of adverse events were high in the ivabradine and placebo groups (75% and 74%, respectively), although this difference was not statistically significant ($p = 0.303$) [Swedberg *et al*. 2010].

Inclusion criteria for the SHIFT trial were patients either on maximally tolerated doses of beta-blockers or those with a contraindication to beta-blocker use. Despite these parameters, only 49% of patients reached at least 50% of the target dose of a beta-blocker before initiation of ivabradine [Swedberg *et al*. 2010]. Patients with HF are frequently unable to achieve optimal beta-blocker dosing due to hemodynamic instability and limited tolerability. Moreover, these adverse effects are often seen in patients with AF on rate-control therapies with beta-blockers, nondihydropyridine calcium channel blockers, and digoxin [January *et al*. 2014]. Since ivabradine reduces HR without associated hemodynamic effects, it may theoretically become an ideal agent for rate control in patients with AF.

In the presented case reports and open-label trial, patients treated with ivabradine as monotherapy or in combination with a beta-blocker had HR reductions. The 2014 ACC/AHA/HRS Guideline for the Management of Patients with AF suggests a target resting HR of less than 80 bpm for symptomatic management, or a lenient rate control of less than 110 bpm if patients are asymptomatic [January *et al*. 2014]. While mean HRs were decreased, it is unclear if targets were achieved due to study design and short duration.

HF is a risk factor for the development of AF. In the AFFIRM study, 23.1% of patients had a history of HF at baseline [Wyse *et al*. 2002]. Ivabradine was originally thought to only influence conduction through the SA node, therefore providing benefit for HF patients but not those with AF. Recent identification of HCN4 (the gene responsible for If current expression) throughout the myocardium suggests this agent may act upon the AV node [Herrmann *et al*. 2011; Ou *et al*. 2010]. The SHIFT trial excluded patients with AF, therefore long-term implications for the use of ivabradine in tachyarrhythmias is unknown, and current product labeling recommends discontinuing ivabradine if AF develops [Swedberg *et al*. 2010]. To date, two case reports and an open-label pilot trial have reported positive results for using ivabradine for HR control in those with AF. Because of its unique mechanism of action on If channels, ivabradine's effect on HR is also being investigated prospectively in chronic heart failure (CHF) patients with permanent AF and prevention of postoperative AF [ClinialTrials.gov identifiers: NCT01796093 and NCT01699776; Abdel-Salam and Nammas, 2016].

Conclusion

HR reduction with ivabradine is achieved through inhibition of I_f channels, previously thought to be solely concentrated in the SA node. Emerging data suggest that ivabradine may reduce conduction through the AV node, and provide HR reduction without associated hemodynamic complications in patients with AF. Morbidity and mortality outcomes, optimal dosing strategy and incidence of adverse effects are unanswered questions warranting further investigation in a larger patient population. Future studies are necessary to determine if

ivabradine will prove to be a useful treatment option for rate control in patients with AF.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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