

Heart Rate Control in Non-Paroxysmal Atrial Fibrillation. A New Indication for Ivabradine?

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ABSTRACT

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with poor quality of life and high rate of hospitalization in elderly frail patients. In patients with non-paroxysmal AF, optimizing heart rate is often the main goal but available drugs fail to reach heart rate control in about 30% of cases and this often happens because their doses can not be implemented due to side effects. Ivabradine is a pure heart rate lowering agent acting through the inhibition of If current in the sinus atrial cells, and it is widely used for patients with

stable angina and chronic heart failure in sinus rhythm. According to very preliminary data, ivabradine shows heart rate lowering properties in non-paroxysmal AF when used alone or in association to other heart rate lowering drugs. Interestingly, studies suggest that this seems to translate into clinical benefits such as improvement of exercise tolerance and ejection fraction. However, new trials are needed to confirm the effectiveness and safety of ivabradine in non-paroxysmal AF.

Key words: Ivabradine; Atrial fibrillation; Heart rate control; Exercise tolerance

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INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia and its incidence and prevalence increase with age. Although by itself it is a non-fatal arrhythmia, it is often associated with a considerable comorbidity and an increased risk of stroke and heart failure. Patients with AF have significantly poorer quality of life than healthy controls, experiencing a variety of symptoms including lethargy, palpitations, dyspnoea, chest tightness, sleeping difficulties, and psychosocial distress^[1]. These symptoms are often related to an uncontrolled ventricular rate and they can be significantly improved by the administration of drugs aimed to establish heart rate (HR) control. In the setting of non-paroxysmal AF, rate-control is an integral part of the management of AF patients as underlined by the most recent guidelines^[2]. In such patients, HR control is usually obtained by using drugs which prolong atrioventricular (AV) node refractoriness such as β -blockers, nondihydropyridine calcium channel blockers, and digoxin. These drugs can be used alone or in combination for resistant AF. In clinical practice the choice of drug and target HR depends on patient characteristics and comorbidities but the decision can be particularly challenging in elderly frail subjects with multiple comorbidities. Diltiazem and verapamil may have negative inotropic effects in patients

with left ventricular ejection fraction under 40%; β -blockers may exacerbate conditions such as asthma or depression, and must be used with caution in cases of hypotension; furthermore, the use of digoxin is restricted in patients with renal failure. Risk of bradycardia and hypotension considerably increases when combinations of these agents (in particular β -blockers and non-dihydropyridine calcium channel blockers) are used. Furthermore, according to current evidences about 20-30% of patients with permanent AF do not reach HR control^[3].

Ivabradine is a pure HR lowering agent currently approved for the treatment of patients with stable chronic angina and heart failure with reduced ejection fraction, in sinus rhythm^[4,5]. Ivabradine effects appear to result from this HR reduction; it does not directly change inotropism or blood pressure.

This review summarizes laboratory findings and clinical data supporting the hypothesis that ivabradine could represent an alternative tool for physicians in order to lower HR and improve clinical conditions of patients with non-paroxysmal AF.

PACEMAKER FUNNY CURRENT IN HEALTHY HEART AND UNDER PATHOLOGICAL CONDITIONS

Ivabradine is a specific inhibitor of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels. HCN channels include a family of cation channels activated by hyperpolarized membrane potentials and stimulated by intracellular cyclic nucleotides. This family consists of four human isoforms with a high homology and common biophysical properties (HCN1-4)^[6,7]. Upon hyperpolarization, all four isoforms generate an inward current (If) in the heart and in the nervous system. Three isoforms (HCN1, HCN2, HCN4) are expressed in cardiac tissues; HCN2 and HCN4 are the dominant subtypes. In the healthy adult heart, HCN channels are predominantly expressed in the conduction system, especially in the sinoatrial (SA) node^[8]. They are responsible for the early phase of diastolic depolarization in these cells and are essential components of cardiac automaticity and HR control^[7].

It has been thought for long time that the function of HCN channels in the heart was limited to cardiac cells belonging to the conduction system and that these channels did not play a significant role in the excitability of non-pacemaking regions in adult atrial and ventricular myocytes^[8,9]. However recent data support the hypothesis that HCN channels expression, and If current density, in cardiomyocytes are amplified when some pathological conditions occur. Cerbai *et al.*^[10] demonstrated that If current occurrence and density are increased in hypertrophic rat cardiomyocytes and that this increase is directly related to the severity of myocardial hypertrophy. Similar results have been confirmed by other authors in animal models of cardiac hypertrophy and heart failure^[11,12]. Stillitano *et al.*^[13] compared the mRNA and protein expression of HCN subunits in the atrium and ventricle of healthy subjects and heart failure patients; they found an up-regulation of ventricular HCN2 and HCN4 underlying the increase in functional If current in heart failure patients.

AF is a pathological condition in which ionic current remodeling has been demonstrated^[14]. Regarding If current, an association between HCN overexpression in atrial and pulmonary vein cardiomyocytes and presence of AF has been reported in animal models and human^[15-18]. In a canine model, He *et al.*^[17] demonstrated that mRNA and protein expression levels of HCN2 and HCN4 in the AF group were significantly increased when compared with the control group. Li *et al.*^[18] analyzed right atrial appendage samples collected from 60 patients undergoing coronary artery bypass grafting; they observed that

mRNA and protein expression levels of HCN2 and HCN4 channels in the right atrial appendage increased with age. Interestingly they also found that these age-associated expression modifications were even more pronounced in aged AF patients compared with aged sinus rhythm patients. In another study on human samples, mRNA levels of HCN4 were reduced in AF compared to sinus rhythm; conversely HCN4 protein expression was similar between the two groups and If current was greater in AF compared to sinus rhythm^[19]. According to these studies, the remodeling response of atrial cardiomyocyte ionic currents that occur during AF also involves If current, but which is the exact role of If current remain still unknown.

Changes in If current may contribute to alter the physiological hierarchy of automaticity and to generate atrial ectopism. However, the exact role of HCN channels in generating and sustaining atrial arrhythmias is not known. Zorn-Paully *et al.*^[20] found that increases in the If current may cause atrial myocytes to function like pacemaker cells, subsequently increasing the local atrial automaticity, decreasing the effective atrial refractory period and enhancing the risk of atrial arrhythmias. Zicha *et al.*^[21] analyzed atrial myocytes in dogs with rapid ventricular pacemaker activity and demonstrated that If enhancement, and the associated HCN channel overexpression, contributed to heart failure-induced ventricular arrhythmias.

Given that if current density is increased during arrhythmias, ivabradine, as an HCN channel inhibitor, could have potential anti-arrhythmic effects. When administered to dogs with age-related AF induced by rapid atrial pacing, ivabradine, by inhibiting if current, increased the effective refractory period of the left pulmonary vein and left atrium, and reduced the duration and inducing rate of AF^[22]. Similar results were obtained on pulmonary vein cardiomyocytes in rabbit^[23] and by El Chemaly *et al.*^[24] who added ivabradine to atrial myocytes isolated from human right appendages of patients undergoing cardiac surgery. These findings suggest that Ivabradine could reduce the cellular automaticity induced by If by inhibiting the HCN channels and the mediated If in pulmonary veins and atrium, and thus potentially prevent the development of arrhythmias such as AF.

IF CURRENT IN THE ATRIOVENTRICULAR NODE

Inside the conduction system a regional difference in expression of various HCN channel mRNAs has been demonstrated^[25]. The expression of all HCN channel mRNA (HCN1-4) is higher in the SA node than AV node^[26], and the most important isoform, HCN4, shows level of expression 6 times higher in the SA node compared to the AV node. Recent studies clarified the role of If current in AV node by demonstrating that the inhibition of this current slows the AV node conduction in animals and humans^[26-30]. Yamazaki *et al.* evidenced that zatebardine, an If current inhibitor, decreased both intrinsic AV rate and the increase in junctional rate in response to sympathetic nerve stimulation in anesthetized dog hearts^[28]. The administration of Ivabradine (0.1 mg/kg IV bolus) slowed ventricular rate (from 240 ± 21 to 211 ± 25 bpm) and increased A-H interval in a rate-dependent fashion^[29]. The administration of Ivabradine and dronedarone, both inhibitors of the If current at AV node level, reduced ventricular rate during AF in pigs by 39.5% (from 200 ± 14.6 to 121 ± 20.1 bpm) and 22% respectively^[26]. Low dose Ivabradine (0.25 mg/kg) reduced ventricular rate during AF in pigs by 9% beats/min ($p = 0.015$) 30 minutes after drug infusion^[31]. This effect was enhanced by the combined administration of ranolazine: when ivabradine was administered shortly after ranolazine, ventricular rate was reduced by 23% beats/min^[31].

Taken together, these results suggest that If current plays a biologically detectable role in the modulation of automaticities of either

isolated or under sympathetic control subsidiary pacemaker cells and support the concept that If current inhibition may provide a novel therapeutic target in the management of AF. These findings, ultimately, opened the way towards a clinical application of If current inhibition in subjects with AF.

CLINICAL EVIDENCES

We conducted an electronic literature search of MEDLINE and EMBASE to identify articles published until November 2016, using the terms “ivabradine” and “non-paroxysmal/permanent atrial fibrillation”. Only studies in English language were included. We found three case reports^[32-34], one open-label trial^[35] and one pilot randomized versus placebo study^[36].

Moubarak *et al.*^[32] suggested for the first time, that Ivabradine might exert clinically-detectable rate-lowering effects in nonparoxysmal AF. They reported the case of a 75 year-old woman who had been previously prescribed Ivabradine while she was in sinus rhythm but that at the moment of the evaluation was in permanent AF. The patient was asked to undergo two 24-hour Holter monitoring: the first was performed while she was taking Ivabradine; the second 7 days after Ivabradine withdrawal. The mean HR was 80.1 bpm on Ivabradine 2.5 mg bid and 87.6 bpm without Ivabradine. However, the value of this first case report was limited by the low quality of the first 24-hour Holter monitoring that forced physicians to restrict the R-R analysis to only a short period of two hours, from 22: 00 to 00: 00, during which the patient was asleep.

Kosiuk *et al.*^[33] administered Ivabradine 10 mg/d to a 59 year old in hospital patient with persistent AF, resting HR over 100 bpm, left ventricular systolic dysfunction that was non-responder to usual medications. The authors observed a progressive decrease of HR over a period of three days of continuous ECG-monitoring: mean HR decreased from 102 bpm to 84 bpm. Moreover they found two intriguing results: firstly maximum HR also decreased from 175 bpm to 144 bpm while minimum HR remained unchanged (from 62 bpm to 59 bpm) suggesting a safe profile for ivabradine use in AF. Secondly in a treadmill test, performed before and after medication, during which the patients reached the same stress level, maximal heart rate during exercise also decreased from 169 to 153 bpm.

Subsequently, the same authors observed similar results in a case series of 5 patients, with mild to severe impairment of left ventricular ejection fraction, treated with ivabradine (5 mg/bid). The drug was used in addition to β -blockers and/or digoxin or alone in those who were intolerant to other drugs^[34]. HR reduction was observed in 60% of cases during a short term follow up of five days.

Our group evaluated 6 subjects with persistent or permanent AF already treated with β -blockers, four patients with carvedilol and two with bisoprolol, and with poor HR control^[35]. Ivabradine was started if HR was > 110 bpm at resting ECG, despite patients were taking the highest tolerated dose of beta-blocker and no further increase was possible. The study follow up was three months. A 24-hour Holter monitoring was performed at baseline and repeated every month. Ivabradine was started at 2.5 mg/bid and the dose was adjusted monthly, according to the results of 24-hour Holter monitoring. Overall we observed that ivabradine determined a significant decrease of median HR in four out of six patients after 3 months of treatment. A similar significant decrease was obtained in maximal and minimal HR. We also observed a dose dependent response: the percentage of responders was 33.2% with ivabradine 2.5 mg/bid and raised to 66.6% at the highest doses. Ivabradine was well tolerated and no side effects occurred during the follow up. Interestingly, no pauses over 2.5 s were observed during 24-hour Holter monitoring. The ivabradine-

dependent HR reduction was associated with significant clinical benefits: there was a significant increase of distance walked at six minute walking test and an improvement in self-perceived dyspnoea index in ivabradine responders compared to nonresponders.

Wongcharoen *et al.*^[36] performed the first randomized double-blind placebo-controlled trial with ivabradine, having as primary end point the change in mean ventricular rate between baseline and 1 month follow up visit. They enrolled 32 patients (90% of whom were on β -blockers) with non-paroxysmal AF and mean HR \geq 70 bpm. Patients were assigned in a 2: 1 ratio to 1 month of treatment with either ivabradine 5 mg bid or placebo. In this study, ivabradine significantly decreased mean 24/h ventricular rate from 86.0 \pm 10.9 bpm to 79.2 \pm 9.6 bpm ($p = 0.001$), while no significant changes in ventricular rate were observed in the placebo group (84.3 \pm 11.2 to 82.9 \pm 9.9; $p = 0.469$) with a significant intergroups difference ($p = 0.024$). The ivabradine-induced HR reduction compared to placebo was more evident during day-time (7.7 \pm 6.2 vs 1.7 \pm 5.8, respectively, $p = 0.014$) than during night-time (5.8 \pm 8.1 vs 1.4 \pm 6.3, respectively, $p = 0.07$). Moreover ivabradine administration was safe: no drug-related adverse effects were observed in both arms.

Overall these preliminary clinical experiences suggest that ivabradine is effective on reducing HR at least in a half of patients with non-paroxysmal AF and show a safe clinical profile. Interestingly, even when added to other HR-lowering agents, ivabradine did not cause symptomatic bradycardia in these patients. However, in our opinion, though no side effects related to the administration of ivabradine in AF have been described yet, too few patients have been treated for too little time and conclusions on this issue cannot be drawn.

POTENTIAL ROLE FOR IVABRADINE IN THE RATE-CONTROL STRATEGY IN NON-PAR-OXYSMAL AF

Rate-control is a well established strategy in the management of non-paroxysmal AF. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial showed that rate-control was non inferior to rhythm-control strategy in term of mortality rate. Moreover, in that study, more patients in the rhythm-control group than in the rate-control group were hospitalized, and there were more adverse drug effects in the rhythm-control group as well. Results from the Rate Control Versus Electric Cardioversion for Persistent Atrial Fibrillation (RACE) study also confirmed that rate-control was equivalent to rhythm-control in the management of nonparoxysmal AF, with rate control offering some potential advantages such as a lower risk of adverse drug effects, a better cost-effectiveness and a decreased incidence of hospitalization^[37].

Among HR lowering agents, β -blockers and nondihydropyridine calcium channel blockers are the first choice: in the AFFIRM trial, they were found to have an overall success rate of approximately 70% for achieving rate control when used either alone or in combination with digoxin. In the study of Fauchier *et al.*^[38], diltiazem 360 mg/day was the most effective drug regimen for reducing the HR and improving arrhythmia-related symptoms in patients with permanent AF.

However, in about 30% of cases, the rate-control strategy fails to reach its target mostly for two reasons: first of all, because patients simply do not respond to the available HR-lowering agents; secondly because many times these drugs cannot be used at all or their use is limited to submaximal doses because of hemodynamic instability or significant comorbidities such as heart failure with reduced ejection

fraction, significant obstructive pulmonary disease or renal failure.

In view of the current limitations of the rate-control strategy in the management of nonparoxysmal AF, we think there is room for new HR-lowering agents to be used in this condition and for therapeutic strategy implementation. In this narrative review, we collected interesting clinical experiences about the use of ivabradine in nonparoxysmal AF that is supported by a growing body of experimental evidences. Despite their promising results, it must be underlined that these data are very preliminary and overall clinical findings supporting the idea of using ivabradine as rate-control agent in nonparoxysmal AF are very scarce. In particular, the total amount of patients treated is very low and there are no consistent follow up data or direct comparisons with other HR-lowering agents. Therefore, the question if ivabradine could be a safe and effective drug in this group of patients still remains largely unanswered.

CONCLUSION

According to recent data ivabradine slows atrioventricular node conduction in animals and humans and seems to be effective in decreasing ventricular rate in subjects with persistent and/or permanent AF. Given its neutral hemodynamic profile, ivabradine has, in our opinion, the potential to become a promising rate-control agent in patients with non-paroxysmal AF, particularly in elderly frail patients. Its combination with other heart rate lowering drugs, particularly with β -blockers, is particularly attractive, mainly for two reasons; firstly, the combination therapy may allow to reach an advisable HR in a greater proportion of patients with nonparoxysmal AF compared to β -blockers alone. Secondly, in frail elderly patients the combination of low doses of two drugs could be better tolerated than high doses of β -blockers. In our opinion, by enhancing HR control and reducing the rate of side effects, ivabradine could lead to positive middle-term and long-term consequences with improvement of clinical stability and exercise tolerance. However, follow up data on effectiveness and safety are still not available. New trials exploring safety of ivabradine alone or in combination with other drugs and its effects on hospitalization rate and other clinical outcomes would be needed in order to better understand its role in non-paroxysmal AF.

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