

## I<sub>f</sub> Current and Heart Rate Control

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### Introduction

Understanding the mechanisms underlying the spontaneous depolarization of cardiac cell membranes, either those of the sinoatrial node or those that may have this ability, such as Purkinje fiber cells in the His bundle, has always been important, because it is the spontaneous depolarization during phase 4 of the action potential that allows these cells to determine a heartbeat, that is to say, act as the heart's natural pacemaker. Moreover, it is through this pathway that the autonomic nervous system regulates heart rate (HR)<sup>1</sup>. That a depolarizing ionic current existed in the Purkinje fiber cells was already known; however, this was erroneously interpreted as a pure K<sup>+</sup> current<sup>2</sup> and thought to disappear during the whole time course of the action potential to be reactivated when the membrane potential reached its minimum value in phase 4. When the I<sub>f</sub> current was discovered in the sinoatrial node, there was doubt as to whether two different currents allowing the existence of a heart's natural pacemaker could be present. But these doubts were dispelled in 1981, when it was demonstrated that both currents were, in fact, identical<sup>3,4</sup>. Thus, it became understood that the heart cell membrane has the ability to depolarize spontaneously and, ever since, this current has been studied with great interest for its ionic, kinetic, and modulatory components<sup>5</sup>.

Molecular biology has made it possible to identify protein subunits, which are the channels through which this ionic current flows; by cloning these subunits, new insights were gained. A new class of ion channels was described: the hyperpolarization-activated cyclic nucleotide-gated (HCN) family, the members of which can be cloned<sup>6-8</sup>. This new family comprises four isoforms distributed in several cardiac and neuronal cells (including retinal cells), the latter being responsible for controlling neuronal excitability<sup>9</sup>. Because sodium currents are more important in phase 1 of cell depolarization, the fact that there is a current of this type in phase 4, activated upon membrane hyperpolarization, earned it the name of *funny* current. Hence, it became known as I<sub>f</sub>, I for current and, for funny. Except for electrophysiologists, most cardiologists were not familiar with this current, until a drug that is both safe and effective for humans was developed to block it. This drug has successfully passed Phase 2 clinical trials. It is interesting, therefore, to review the electrophysiological

mechanisms involved in cell depolarization in order to understand how the I<sub>f</sub> works, how it can be blocked, and what studies have been done on this blockade.

### I<sub>f</sub> current

The depolarization of sinoatrial nodal cells is voltage-dependent, occurring in phase 1 of membrane depolarization after the voltage threshold has been reached (about -60mV), when calcium channels open (Figure 1). During this process, sodium channels, which are activated at potential levels much closer to zero, also open, unlike the sodium channels in Purkinje cells, which are activated at rather lower levels (between -90 and -70 mV) and trigger their phase 1 of rapid depolarization. During phases 2 and 3 of repolarization several channels are activated, basically with influx of potassium into the intracellular space and efflux of sodium and calcium to the extracellular space, causing the membrane potential to return to its resting electrochemical gradient. In phase 4, there is a slow, gradual depolarization up to the threshold in which calcium channels are reactivated and depolarization occurs. The I<sub>f</sub> current, which depends on sodium and potassium ion channels, accounts for this spontaneous membrane depolarization (Figures 2 A and B). Of course this current is affected by several stimuli that act on these ion channels, such as the sympathetic and parasympathetic (Figure 3). Thus, beta<sub>1</sub> receptor stimulation increases the I<sub>f</sub> current, whereas vasovagal stimulation, through muscarinic cholinergic nerve terminals reduces it<sup>7</sup>. This current, unlike other known currents, is activated from a threshold of -40 to -50mV and reaches maximal activation between -100 and -110 mV, and it allows ions to enter the cell. It activates slowly upon membrane hyperpolarization (phase 4), and the more negative the membrane potential difference is, the faster the ionic flow. The time constant of the I<sub>f</sub> current is one second at -55 mV, shortening by 0.5 seconds at -75 mV and rapidly

### Key words

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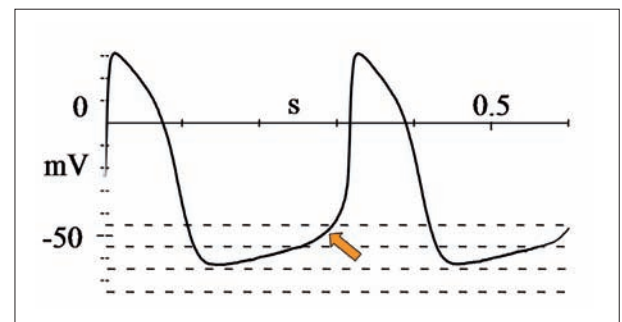


Fig. 1 - Action potential of the sinoatrial node cells. Depolarizing current depends basically on calcium influx. In phase 4, the potential difference decreases progressively until the threshold is reached (-50 mV), when depolarization occurs (arrow).

## Clinical Update

deactivating after membrane depolarization, between +15 and +30 mV, during the action potential plateau (Figure 2B). Several interferences in this current functioning have already been described, but the most important are the following: 1) modulation of the I<sub>f</sub> current by the sympathetic system, changing its flow velocity and, thereby, the frequency of membrane depolarization (Figure 3)<sup>8</sup>, 2) the blockade of I<sub>f</sub> channels alters the rate of cell membrane' spontaneous diastolic depolarization.

### I<sub>f</sub> current blockade

The existence of an ionic current implies the presence of channels that allow ions to pass through the cell membrane. The blockade of these channels that carry I<sub>f</sub> current was demonstrated in rabbit sinoatrial node cells<sup>11-13</sup>. The degree of this blockade and, therefore, its capacity to decrease the frequency of membrane depolarization, vary according to the membrane action potential. Particularly with zatebradine<sup>12</sup>, a reasonably specific blocker of the I<sub>f</sub> current, the more negative

the voltage, exactly when ion influx is higher, the greater the blockage. Therefore, the greater the ion influx the greater its ability to reduce depolarization frequency and vice-versa. It has also been demonstrated that this blockage only occurs when the channels are open. By decreasing depolarization frequency of the sinoatrial node this agent decreases heart rate.

### Ivabradine

This molecule, a benzocycloalkane derivative, has a high degree of specificity for I<sub>f</sub> current inhibition and exclusively lowers HR significantly (Figure 4). In addition to being much more selective than zatebradine and other I<sub>f</sub> current blockers, it exerts its effect at a much lower concentration<sup>13-15</sup>. Similar to zatebradine, ivabradine acts at the intracellular side of the membrane<sup>15</sup> and requires open channels to exert its blocking action. At near-to-zero voltages, when channels are closed, no effect is observed with this drug. Experimentally, ivabradine action has shown to be much more potent in the presence of outward currents than in the presence of inward currents.

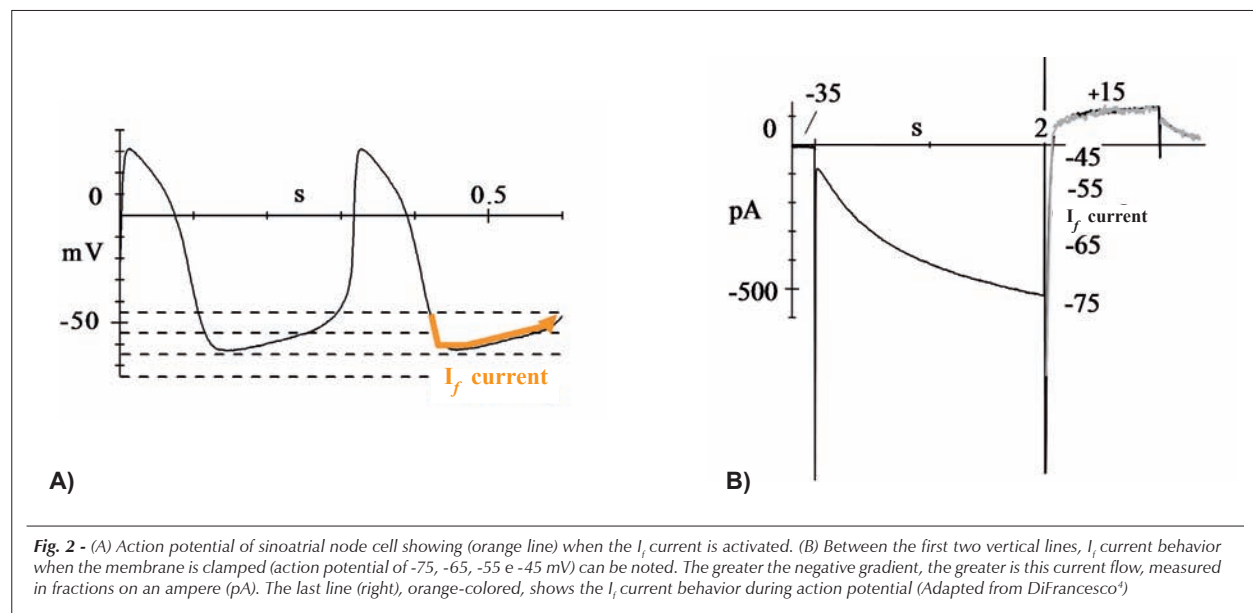


Fig. 2 - (A) Action potential of sinoatrial node cell showing (orange line) when the I<sub>f</sub> current is activated. (B) Between the first two vertical lines, I<sub>f</sub> current behavior when the membrane is clamped (action potential of -75, -65, -55 e -45 mV) can be noted. The greater the negative gradient, the greater is this current flow, measured in fractions on an ampere (pA). The last line (right), orange-colored, shows the I<sub>f</sub> current behavior during action potential (Adapted from DiFrancesco<sup>7</sup>)

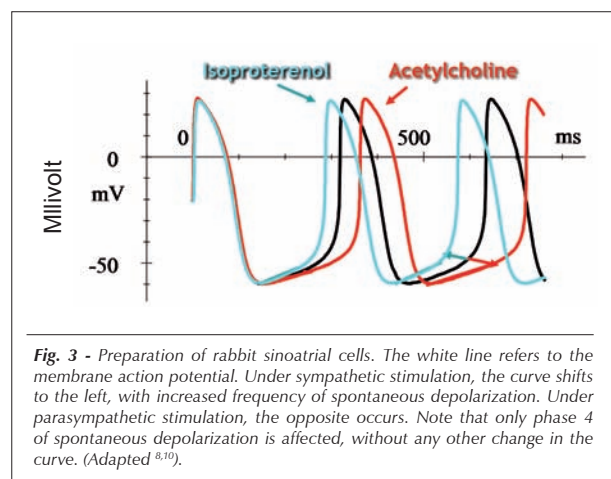
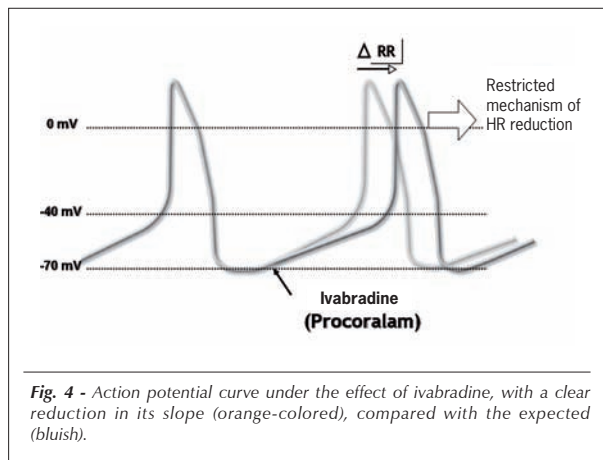


Fig. 3 - Preparation of rabbit sinoatrial cells. The white line refers to the membrane action potential. Under sympathetic stimulation, the curve shifts to the left, with increased frequency of spontaneous depolarization. Under parasympathetic stimulation, the opposite occurs. Note that only phase 4 of spontaneous depolarization is affected, without any other change in the curve. (Adapted<sup>8,10</sup>).

Therefore, it is clear that ivabradine block is not only voltage-dependent or channel-state dependent.

The effect of ivabradine has sparked interest for use in humans, because HR reduction is the primary aim in some situations, particularly in patients with coronary disease, since heart rate is the major determinant of myocardial oxygen uptake. Moreover, the possibility of achieving cardiovascular protection by lowering HR also brought perspectives for its use, especially because, unlike beta-blockers, ivabradine is devoid of inotropic or any other hemodynamic systemic effect. On the other hand, its effect remains unchanged even under adrenergic stimulation, although it has no effect on β-adrenergic receptors. In experimental models using isolated rat atrial cells, HR was reduced by up to -34% and in rabbits, by -24%. In these studies, almost no variation was found in either duration or amplitude of cell membrane action potential. All



findings in the sinoatrial node and Purkinje cells corroborate the absence of any effect by ivabradine to cause calcium channel blockade. Furthermore, in experimental studies using dogs undergoing treadmill exercise, ivabradine did not affect the natural increase in cardiac output and contractility during exercise nor was there change in coronary vasodilation capacity, unlike propranolol, used as a comparator in these experiments<sup>16</sup>. Given these results, a clinical program was developed to evaluate the effect of this drug in humans, in compliance with the stringent requirements currently applied to studies of any new drug.

**Clinical trials in stable angina** – After Phase I trials<sup>17</sup>, a large Phase II trial confirmed that ivabradine lowers HR both at rest and during exercise<sup>18</sup>. In this study, 360 patients with stable angina and documented CAD were randomly assigned, in a double-blind fashion, to receive one of three doses of ivabradine (2.5mg, 5mg, or 10mg twice daily) or placebo. The study's primary endpoint was to assess, by using exercise tolerance test, the time to onset of ST-segment depression on electrocardiogram (ECG) and time to limiting angina at the trough of drug activity, that is, 12 hours post-dose. As secondary endpoints, the following parameters were assessed: HR and double product, both at rest and at peak exercise, ECG data four hours post-medication, plus angina frequency and sublingual nitrate consumption. The study design comprised a two-week treatment in one of the four above-mentioned groups followed by a two- or three-month open-label follow-

up phase during which all patients received ivabradine 10 mg twice daily. Drug safety was assessed through routine laboratory tests, the frequency of adverse events, and vital signs, in addition to 24-hour ECG Holter monitoring. During the two-week treatment period, ivabradine 5 and 10 mg BID increased significantly the time to onset of ST-segment depression by 44 s e 46 s, respectively, compared to 9 s for the placebo group ( $p < 0.005$ ). The dose effect was also significant ( $p = 0.005$ ), but the effect of the 2.5 mg dose did not differ from that of the placebo. In the two- to three-month open-label extension phase, those who were initially in the placebo group also experienced a significant decrease in the number of angina attacks and ischemia and an increase in time to limiting angina, with  $p < 0.001$ . The benefits observed were associated with the degree of HR reduction induced by ivabradine. Additionally, the tolerability profile was good, and the only major adverse event was visual disturbance reported by up to 27% of the patients in the ivabradine 10 mg BID group, mostly changes in light intensity perception, described as mild and transient. Other studies, which have already been concluded but are still to be published, compared ivabradine with two common antianginal drugs, the  $\beta$ -blocker atenolol<sup>19</sup> and the calcium-channel antagonist amlodipine<sup>20</sup>. In both studies, ivabradine was shown to be as effective as atenolol and amlodipine in controlling anginal symptoms and increasing the time to ischemia during exercise testing. Two clinical trials are currently underway: one to assess both the efficacy and safety of ivabradine in patients receiving background therapy with atenolol and the other to assess the effect of HR lowering in patients with heart failure secondary to ischemic heart disease or dilated cardiomyopathy, in order to check whether the additional HR reduction may have a beneficial effect on cardiovascular events and death. Based on all this information and knowing that a reasonably large number of individuals with contraindication, or much more frequently, intolerance to  $\beta$ -blockers, such as patients with chronic pulmonary disease, asthma, peripheral vascular insufficiency, diabetes mellitus, gastrointestinal changes, and keratitis, as well as intolerance to calcium antagonists that slow heart rate, such as patients with obstipation, lower-extremity edema, and hypotension, among others, it can be concluded that ivabradine is a very attractive option as an antianginal agent, particularly because it lowers HR without exerting hemodynamic effects and has a very good tolerability profile.

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