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Review Article

Heart Rate Slowing by *If* Inhibition

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ABSTRACT

The slow diastolic depolarization phase in cardiac pacemaker cells is the electrical basis of cardiac automaticity. The hyperpolarization-activated current (*I*f) is one of the key mechanisms underlying diastolic depolarization. Particularly, *I*f is unique in being activated on membrane hyperpolarization following the repolarization phase of the action potential. *I*f has adapted biophysical properties and voltage-dependent gating to initiate pacemaker activity. *I*f possibly constitutes the first voltage-dependent trigger of the diastolic depolarization. For these reasons, *I*f is a natural pharmacological target for controlling heart rate in cardiovascular disease. In this view, *I*f inhibitors have been developed in the past, yet the only molecule to have reached the clinical development is ivabradine. At the cellular level, the remarkable success of ivabradine is to be ascribed to its relatively high affinity for f-channels. Furthermore, ivabradine is the most *I*f-specific inhibitor known to date, since moderate inhibition of other voltage-dependent ionic currents involved in automaticity can be observed only at very high concentrations of ivabradine, more than one order of magnitude from that inhibiting *I*f. Finally, the mechanism of block of f-channels by ivabradine has particularly favorable properties in light of controlling heart rate under variable physiological conditions. In this article, we will discuss how *I*f inhibition by ivabradine can lead to reduction of heart rate. To this aim, we will comment on the role of *I*f in cardiac automaticity and on the mechanism of action of ivabradine on f-channels. Some aspects of the cardiac pacemaker mechanism that improve the degree of security of ivabradine will also be highlighted.

INTRODUCTION

If (Ionic current F) Current: 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). That a depolarizing ionic current existed in the Purkinje fiber cells was already known; however, this was erroneously interpreted as a pure K^+ current 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*f* 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. 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. 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. This new family comprises four isoforms distributed in several cardiac and neuronal cells (including retinal cells), the latter being responsible for controlling neuronal excitability. 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*f*, I for current and *f* 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*f* works, how it can be blocked, and what studies have been done on this blockade[1,2].

The fundamental discovery of the pacemaker $\boldsymbol{I}_f$ current: The heart beats rhythmically thanks to the existence of a special "engine": the sinus node, called "the natural pacemaker". The cells of the sinus node are able to generate a spontaneous regular action potential and thereby modulate heart rate.

In the late 1970s, Dario DiFrancesco started to study the cellular mechanisms governing the generation of this spontaneous electrical activity in the sinus node. This led to the discovery of a major ionic current that is responsible for the generation of spontaneous activity, the $\boldsymbol{I}_f$ current. In a paper published in Nature in 1979 along with Hilary Brown and Susan Noble (Brown, DiFrancesco & Noble, 1979), DiFrancesco and collaborators described for the first time this $\boldsymbol{I}_f$ current,

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the "f" standing for "funny". It was called "funny" because it had very unusual properties when compared to other cardiac currents known at the time. It is since considered as one of the most important ionic currents for the generation and control of heart rate[1].

It is established that heart rate is a key determinant of cardiac ischemia. In the last decade, growing evidence has emerged from large-scale epidemiological studies that elevated heart rate is associated with an increased risk of cardiovascular events. This association has been reported in apparently healthy individuals and in patients across the cardiovascular disease spectrum. The relevance of the I_f current in the generation of heart rate and its control made it an ideal target to develop new drugs aiming at selectively reducing heart rate[3].

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. 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*f* current, which depends on sodium and potassium ion channels, accounts for this spontaneous membrane depolarization (Figures 1).

Of course this current is affected by several stimuli that act on these ion channels, such as the sympathetic and parasympathetic (Figure 2). Thus, beta-1 receptor stimulation increases the I*f* current, whereas vasovagal stimulation, through muscarinic cholinergic nerve terminals reduces it. 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*f* current is one second at -55 mV, shortening by 0.5 seconds at -75 mV and rapidly deactivating after membrane depolarization, between +15 and +30 mV, during the action potential plateau. Several interferences in this current functioning have already been described, but the most important are the following:

1.modulation of the I*f* current by the sympathetic system, changing its flow velocity and, thereby, the frequency of membrane depolarization (Figure 2),

2.the blockade of I*f* channels alters the rate of cell membrane' spontaneous diastolic depolarization[4,5].

Importance of *I*f in the Autonomic Regulation of Pacemaker Activity: *I*f is also one of the major effectors for promoting autonomic control of pacemaker activity. For our purposes, it is important to keep in mind that *I*f has the capability to respond to a small increase/decrease in intracellular cAMP by positively or negatively shifting its voltage dependence. As a consequence, even small changes in the cAMP concentration can result in significant changes in the rate of pacemaking. In this respect, it has been proposed that *I*f constitutes the major mechanism to both reduce the heart rate at low parasympathetic tone and to quicken the heartbeat under moderate activation of the Beta-adrenergic receptor. This proposal is based on the observation that low doses of ACh or of the Beta-adrenergic agonist isoproterenol specifically decrease and increase the slope of the diastolic depolarization in the absence of an effect on the action potential shape. We can thus think to f-channels as both an accelerator and brake of the heart rate in the everyday life of the individual. The importance of f-channels in the autonomic regulation of the heart rate has recently been confirmed in a human subject carrying mutations in the HCN4 gene. This mutation (named 573X) generates a truncation at the C-terminal part of the channel protein and induces a loss of the exercise-induced increase in heart rate. Another mutation in the human HCN4 gene is associated with familial asymptomatic bradycardia. Affected HCN4 channels are normally responsive to cAMP, but activate for more negative voltages than wild-type channels. Interestingly, this mutation induces a moderate reduction of the basal heart rate leading the authors to propose that this mutation has functional effects similar to that of low doses of ACh. These observations are consistent with the view that manipulations of the activity of f-channels can effectively regulate heart rate without disrupting the pacemaker mechanism or inducing life-threatening arrhythmias[6-8].

*I*f and Cardiac Pacemaking: Heart automaticity is generated by a small population of modified myocytes located in the SAN. Automaticity in pacemaker cells is due to the diastolic depolarization (also named pacemaker potential), a slow depolarizing phase of the action potential, which leads the membrane potential at the end of an action potential to the threshold of the following action potential. Diastolic depolarization develops during the diastole of the cardiac contraction cycle and is a hallmark of cardiac automatic cells. The atrioventricular node and the Purkinje fiber network can also generate viable pacemaker activity. However, due to its intrinsic higher firing rate, the SAN suppresses pacemaking of the CCS and controls the overall heart rate. Even if pacemaker activity of the conduction system in vivo is normally suppressed by the dominant firing frequency of the SAN, it can become dominant in case of SAN failure or block of the atrioventricular conduction. *I*f is associated with the genesis of automaticity throughout the heart development. Indeed, it is important to note that in the embryo, before the development of the CCS, myocardial cells generate their own pacemaker activity. For example, during the development of the mouse heart, *I*f is expressed in the whole myocardial tissue and is associated with automaticity. After the development of

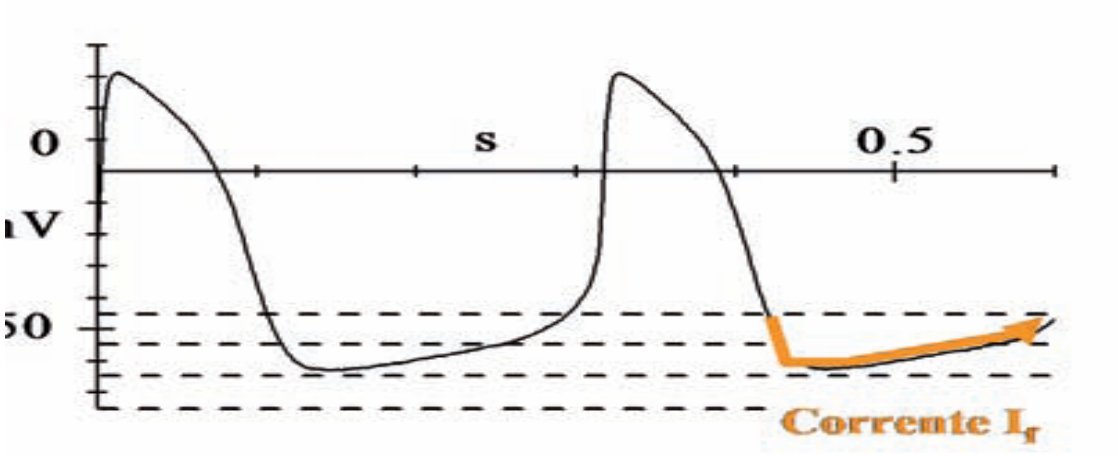

Figure:1.Action potential of sinoatrial node cell showing (orange line) when the If current is activated.

the CCS, the working myocardium loses its pacemaking properties and the SAN takes over the chronotropic control of the heartbeat. The expression of *I*f is drastically downregulated in the myocardium at the end of the development and becomes restricted to the mature CCS. It would be interesting to know at which point of the heart development *I*f becomes important for pacemaking since early candidate precursors of pacemaker cells beat in the absence of functional voltage-dependent ionic channels. In this respect, one of the most intriguing finding in embryonic hearts lacking HCN4 channels is the lack of mature differentiated pacemaker cells in the heart. Indeed, only cells showing early embryonic pacemaking can be found in HCN4-deficient hearts. This observation is suggestive of a key contribution of HCN4 channels in the development of the pacemaker cells and the CCS. In contrast to early precursor pacemaker cells, automaticity in mature pacemaker cells is generated by the association of different classes of ionic channels. Indeed, pacemaker activity in the adult can be viewed as the sum of the activity of different classes of ionic channels playing specific physiological roles . Since biological evolution has based the mammalian cardiac pacemaker on a concerted ionic mechanism, it is possible to target *I*f for controlling heart rate without impairing automaticity per se. Numerical simulations of pacemaker activity can illustrate this point in a visually pleasant way. From this simulation of mouse SAN pacemaker activity, it can be viewed that *I*f is activated in the diastolic depolarization range and supplies inward current which contributes to counterbalancing the decaying fast component of the delayed rectifier (*I*Kr) close to the maximum diastolic potential, as experimentally shown in rabbit pacemaker cells. Beside *I*f, the T- and L-type Ca2_ currents (*I*Ca,L and *I*Ca,T) activate during diastolic depolarization and contribute to the setting of the pacing rate. *I*Ca,L is also responsible for the upstroke phase of the action potential and regulates the action potential duration by opposing to the repolarizing action of *I*Kr. The fundamental importance of *I*f is thus linked to its property of being activated upon hyperpolarization. Thanks to this, *I*f is the first voltage-dependent mechanism which opposes to *I*Kr after the repolarization phase, thereby initiating diastolic depolarization and allowing the proper recruitment of *I*Ca,T, *I*Ca,L as well as other voltage-dependent channels which are all activated upon depolarization. This is the reason why specific pharmacological inhibition of *I*f reduces the slope of the early and late diastolic depolarization phase (Figure. 3). *I*f also constitutes a safety guard mechanism in pacemaker tissue that naturally opposes to membrane hyperpolarization induced by muscarinic K^+ channels (*I*KACh) or in ischemic conditions. Consistent with this view, all known pharmacological inhibitors of f-channels, including ivabradine, induce moderate negative chronotropism in both intact SAN tissue and in isolated pacemaker cells. Consistently, the heterogeneous regional distribution of *I*f influences the sensitivity to different f-channel blockers of pacemaker activity in the center and in the periphery of the SAN. For example, the negative chronotropic effect of Cs_ and UL-FS 49 is more pronounced in the periphery of the SAN than in the dominant center region. The capability of *I*f to set the heart rate is also strikingly demonstrated by genetic evidence. Indeed, in a large-scale mutagenesis study in zebrafish, a study in which mutant strains were selected for mutations affecting the cardiovascular system, a mutant named '*slow mo*' *(smo)* was identified by virtue of the reduced heart rate observed in embryos . More precisely, isolated heart cells from *smo* embryos have downregulated *I*f due to abolition of its fast kinetic component. The functional association between abolition of the fast component of *I*f and bradycardia in *smo* zebrafish mutants constitutes strong evidence of the importance of f-channels in the determination of heart rate. Finally, the capability of f-channels to initiate automaticity constitutes the basis of the development of so-called 'biological pacemakers'. This approach is based on the observation that overexpression of HCN2 or HCN4 channels in cultured neonatal ventricular myocytes strongly enhances automaticity. Consistent with the view that *I*f initiates pacemaking in these myocytes, suppression of HCN channel expression by a dominant negative HCN2 subunit abolished automaticity. It has been shown that adenoviral gene transfer of HCN2 channels in vivo in the canine left atrium induces expression of *I*f in atrial myocytes and is able to generate viable supraventricular rhythms. This strategy has now been modified to obtain a

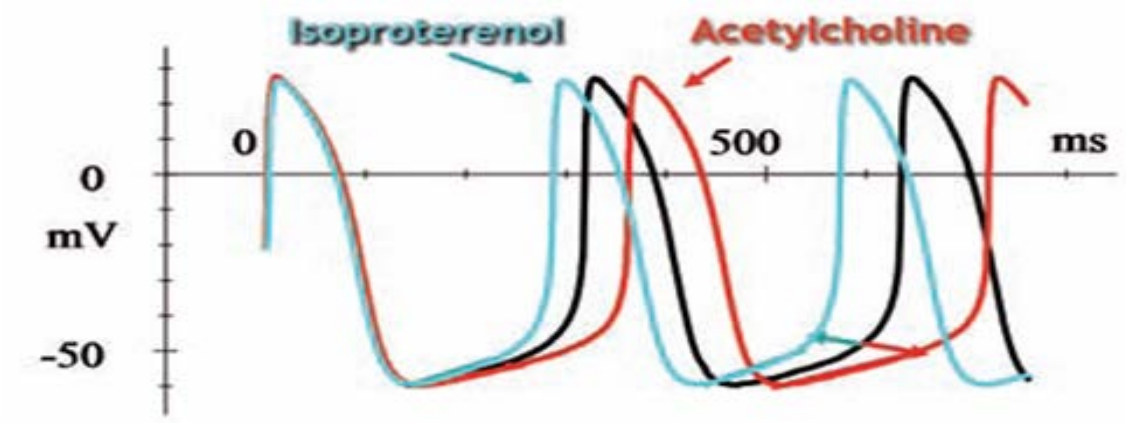

Figure:2 Preparation of rabbit sinoatrial cells

specific gene transfer in the CCS, rather than in the myocardial tissue[9-13].

If current inhibition: Pharmacological inhibition of *i*f as therapeutically effective tool- Controlling heart rate in cardiovascular disease is one of the major goals to limit cardiac ischemia, ameliorate patient's everyday life and improve long-term survival. The main challenge in this approach is to reduce heart rate in the absence of negative side effects on cardiac contractility. Even if heart chronotropic and inotropic mechanisms are anatomically and functionally separated, the possibility of modulating heart rate in a specific way has long been limited by the lack of knowledge about the physiological mechanisms underlying cardiac automaticity. However, during the last 20 years, electrophysiology of cardiac pacemaker cells has put into evidence the relevance of ionic channels in cardiac automaticity and particularly, the specific role of the 'pacemaker' current *I*f in the genesis and autonomic regulation of heart automaticity. The possibility of targeting *I*f for controlling heart rate has thus become a new concept in the pharmacological treatment of cardiac ischemic disease. By the theoretical point of view, a specific heart-rate-reducing agent should influence only the duration of the diastole with no effect on either heart contractility or repolarization. Ivabradine has been shown to fulfill all these requirements and can constitute a new reference molecule for further development of heart-rate-reducing agents. Ivabradine is a heart-rate-reducing agent developed for the treatment of stable angina pectoris. It specifically inhibits *I*f and limits exercise-induced tachycardia in the absence of inotropic or dromotropic effects in all animal models tested thus far. Ivabradine administered at pharmacological doses to experimental animals does not affect the corrected QT interval . As expected from a pure effect on the diastolic phase of the cardiac cycle, the consequence of heart rate reduction is an improved balance between myocardial oxygen demand and supply. At the cellular level, ivabradine induces negative chronotropism in pacemaker cells by decreasing the rate of diastolic depolarization. Here we will discuss the cellular mechanism of action of ivabradine with respect to the functional role of *I*f in pacemaking and put into evidence the importance of *I*f inhibition for modulating heart rate[14-16]. Few agents were developed for inhibition in the past; the first of which is Alinidine, a clonidine derivative, that was soon abandoned due to its relative inotropic action. Later, zetabradine, a benzazepinone derivative also went out of contention due to unacceptable ocular side effects and QTc prolongation[17].

Ivabradine, a unique specific current inhibitor, was first described by Thollon et al. more than a decade ago. It exhibit dose-dependent heart rate reduction with minimal effect on myocardial contractility, blood pressure, intracardiac conduction and ventricular repolarisation. At the treatment dose, ivabradine has no effect on electrocardiographic PR or QT (QTc) interval. When compared with beta-blocker atenolol, ivabradine depresses myocardial relaxation to a lesser extent both at rest and exercise[18].

Action of Ivabradine at the Cellular Level: Evidence of the action of ivabradine on cardiac automaticity came from in vitro studies in isolated spontaneously beating rat right atria. Indeed, ivabradine reduced the rate of pacing of these preparations in a dose-dependent way. This result was strongly suggestive of an effect of the drug on SAN automaticity and prompted further in vitro studies on rabbit SAN tissue preparations and isolated pacemaker cells. Particularly, using isolated rabbit SAN pacemaker cells, it has been demonstrated that ivabradine reduces pacemaker activity by decreasing the slope of the diastolic depolarization, without significantly affecting the cell maximum diastolic potential. Dose-dependent reduction of the slope of the diastolic depolarization is paralleled by progressive inhibition of *I*f in a similar range of concentrations of ivabradine. Indeed, the IC50 for reduction of pacemaker activity and *I*f inhibition are consistent between 1.5 and 3_M. These observations on isolated rabbit SAN cells have recently been confirmed also in mouse SAN cells. For concentrations close to the IC50 for *I*f, no effect was observed on *I*Ca,L, *I*Ca,T and *I*Kr. Moderate inhibition of *I*Ca,L (16%) and *I*Kr (18%) have been observed at 10_M ivabradine, when *I*f is blocked at about 90%. Such moderate effects on *I*Ca,L and *I*Kr at high doses of ivabradine are unlikely to have any supplementary impact on pacemaker activity, since

numerical simulations of rabbit SAN pacemaking indicate that no alterations of the action potential waveform are observed when these effects are included in calculations. These data demonstrate the specificity of ivabradine action on f-channels in pacemaker cells[17,19,20].

Mechanism of Action of Ivabradine on f-Channels: Electrophysiological recordings on isolated SAN pacemaker cells using the patch-clamp technique have demonstrated use- and current-dependent inhibition of *I*f by ivabradine. In this respect, the action of ivabradine on f-channels differs from that of other *I*f blockers such as UL-FS49. Indeed, *I*f inhibition by UL-FS49 is also use dependent, but block does not depend on the current driving force. Ivabradine reduces the total *I*f conductance without affecting its voltage dependence, indicating that the drug does not alter the capability of the gating mechanism to sense the membrane voltage. Ivabradine enters the f-channel mouth by the intracellular side of the membrane thereby interfering with transmembrane ionic flux. Consistent with this view, native SAN f-channels must be in the open state for being blocked by ivabradine. The current-dependent block of *I*f by ivabradine is an interesting phenomenon. Particularly, current dependency of block reveals competition of occupancy in the pore of the f-channel between Na^+ and K^+ ions and ivabradine. Consequently, when both Na^+ and K^+ permeate the channel from outside the membrane at negative voltages below the K^+ equilibrium potential, ivabradine will be effectively 'pulled out' from the channel inner mouth. Inversely, when net outward current flows through f-channels, the efficacy of block by ivabradine will be maximal. In the pacemaker cycle, ivabradine will thus preferentially inhibit *I*f at positive voltages, during the diastolic depolarization and repolarization when f-channels deactivate. Use dependency of block will also favor *I*f inhibition at a high pacing rate, when control of heart rate is more useful. Importantly, release of f-channel block at lower heart rates or when the maximum diastolic potential undergoes spontaneous hyperpolarization (e.g. during enhanced vagal tone) can constitute a supplementary safety mechanism to counteract excessive slowing of heart rate. We can expect that ivabradine might also be useful in the diseased myocardium in conditions where *I*f expression is enhanced and has been proposed to have potential proarrhythmic effects. Indeed, it could be possible that block of *I*f in the atria might prevent the onset of atrial fibrillation[7,8].

Main Pharmacological Results for Cardiac Protection with Ivabradine: The effect of ivabradine on coronary perfusion has been investigated in resting and exercising conscious dogs and compared with the Beta-blocker propranolol. Ivabradine reduced resting and exercising heart rate in a dosedependent manner and preserved coronary artery vasodilatation during exercise without any negative inotropic effects. In contrast, for the same heart rate reduction, propranolol caused vasoconstriction of the coronary arteries and a negative inotropic effect. The same study showed that ivabradine does not alter the increased cardiac output and stroke volume upon exercise, which were significantly decreased by propranolol. Finally, this study proved that the coronary and systemic effects of ivabradine were exclusively due to its effect on heart rate as they were abolished by atrial pacing. Therefore, ivabradine reduces heart rate, preserves coronary vasodilatation upon exercise, i.e. myocardial perfusion, with no negative inotropic effects and maintenance of cardiac contractility. Ivabradine's anti-ischemic properties also effectively ensure a better cardiac recovery upon reperfusion. In a recent study in our laboratories, we have shown that administration of ivabradine preserves tissue ATP levels in the isolated perfused rabbit heart during ischemia and reperfusion. This cardioprotection is dependent on ivabradine's heart-rate-lowering activity because it disappears upon atrial pacing and it is dose dependent. These results confirm previously reported findings in another experimental model study with a Beta-blocker. Equally, ivabradine decreases, in a dose-dependent manner, myocardial oxygen consumption assessed in experimental studies by measuring the difference in quantity of oxygen between aortic and coronary sinus blood. In addition, ivabradine does not affect the ratio between oxygen delivery-consumption, thus preserving coronary artery dilatation. The protection of the ischemic myocardium by heart rate reduction has been tested for ivabradine and atenolol in an animal model of exercise-induced ischemia and stunning. Ivabradine and atenolol reduced heart rate to the same extent at rest and during exercise. During exercise, ivabradine improved left ventricular wall thickening (antiischemic effect) and reduced the subsequent myocardial stunning compared with saline. The Beta-blocker also improved left ventricular wall thickening, but had no effect on stunning. The effect of ivabradine disappeared upon atrial pacing, proving that it is solely due to ivabradine's heart-rate-reducing properties and can be linked to the improvement in myocardial contractility. Atenolol appeared to be rather deleterious on stunning. Ivabradine has also been shown to improve left ventricular dysfunction in congestive heart failure and to reduce remodelling subsequent to myocardial infarction. In postmyocardial infarction rats, heart rate reduction with ivabradine decreased left ventricular collagen density and increased left ventricular capillary density, without modifying left ventricular weight, indicating that heart rate reduction improves left ventricular function, increases stroke volume, and preserves cardiac output. This improvement in cardiac function was related not only to the heart rate reduction per se but also to the modification of the extracellular matrix and the function of the myocytes as a result of the longterm reduction in heart rate. These observations have been tested clinically using ivabradine in coronary artery disease patients with left ventricular dysfunction (ejection fraction _40%) with promising results . These results may be linked to modifications of left ventricular structure. Increased heart rate and hemodynamic forces may play a role in plaque disruption. Plaque rupture is the main pathophysiological mechanism underlying acute coronary syndromes and the progression of coronary atherosclerosis. The role of hemodynamic forces, i.e.

heart rate, has been investigated in 106 patients who underwent two coronary angiographic procedures within 6 months. This study identified positive associations between plaque rupture, left ventricular muscle mass 270 g, and mean heart rate 80 bpm and a negative association with heart-rate-reducing treatment[21,22].

Potential Pharmacological Benefits of *I*f Inhibition beyond Heart Rate Control: F-channels have been identified not only in the sinus node but also in the diseased ventricle of experimental animals with heart failure or in ventricular biopsies of patients transplanted for ischemic or dilated cardiomyopathies. The presence of f-channels in ventricular myocytes is intriguing, and relates to pathophysiology rather than to physiology. In fact, the first recordings of the *I*f current in normal guinea pig ventricular cardiomyocytes (VCMs) ruled out any possible physiological role for this current, which was much smaller than in the sinus node, and activated at voltages far from normal resting potentials(i.e. more negative than -100 mV) . The situation, however, appears to be quite different in heart disease, since f-channels are upregulated in a variety of animal models of cardiac hypertrophy and failure; in those circumstances, a functional role becomes apparent and a clear-cut diastolic depolarization can be detected in ventricular myocytes isolated from the diseased ventricles of those animals. Relative increase in current density (diseased vs. control VCMs) in several rat models of cardiomyopathies as well as in human ischemic and dilated cardiomyopathies. Current density is a convenient way to normalize current amplitude with respect to cell size, as cardiomyocytes are 'hypertrophic'. f-channels were at least doubled in left VCMs from rats with mild or severe cardiac hypertrophy caused by pressure overload, and in rats with overt heart failure caused by high blood pressure or postmyocardial infarction. The degree of hypertrophy positively correlated with an increased f-channel density and changes in expression levels were most pronounced in those cardiac regions with highest overload (a finding that was confirmed in our lab), indicating that the processes leading to hypertrophy directly affected the level of hyperpolarization-activated cyclic nucleotidegated channel expression. In addition to electrophysiological data, molecular biology techniques have evidenced a parallel upregulation of mRNA levels, of isoforms underlying ventricular channels not only in the diseased rat heart but also in the hypertrophied hearts of mice overexpressing $Beta_2$-adrenoceptors. *I*f recorded in nonpacemaker regions of the heart shows electrophysiological properties (voltage dependence, kinetics of activation, Na/K permeability ratio) qualitatively similar to those described 20 years ago by DiFrancesco et al. for primary and subsidiary pacemakers. It was proposed that mislocalized expression and/or overexpression of cardiac f-channels may represent an example of a general phenomenon, termed cardiac remodelling, which also consists in the re-expression of fetal proteins. In fact, f-channels are present in fetal and neonatal ventricular myocytes and lose their capacity for generating spontaneous activity during electrophysiological maturation toward adult phenotype. From a clinical point of view, the most interesting aspect of this phenomenon is that the *I*f current may represent an arrhythmogenic mechanism in heart failure, a condition associated with high risk of sudden cardiac death. Another possibility is that the *I*f current is implied in determining the transition from the adult to the embryonic genetic program, leading to reinstatement of cardiac apoptosis and subsequent remodelling of the ventricle[23,24].

Side Effects: Phosphenes**:** The visual effects, especially those induced by ivabradine, have been extensively investigated in both animal models and humans. Ivabradine is a novel antianginal drug that reduces heart rate by inhibiting the hyperpolarization-activated current expressed in cardiac sino-atrial node cells (I_f). During the non-clinical visual safety program, no toxic damage in any ocular structure has been reported in animal models upon administration of therapeutic doses for humans. The visual symptoms induced by ivabradine, reported by patients during the clinical programme, include most commonly phosphenes (14.5% of patients) and less frequently blurred vision. Visual effects appear generally within the first 2 months of treatment and their frequency increases with the dose of ivabradine. Most of these events were reported to occur in conditions of darkness or dim light, when the retinal sensitivity is high. Phosphenes are generally reported to be mild or moderate and to disappear even though treatment continued (77.5% of patients) or after treatment cessation. The host plausible hypothesis is that ivabradine interacts with the visual system by inhibiting hyperpolarization-activated current in retinal cells (I_h)[8].

CONCLUSION

We can expect a number of clinical benefits from pure heart reduction in coronary patients. Pure heart rate reduction by specific and selective *I*f inhibition decreases oxygen demand and improves myocardial energetics; it increases diastolic perfusion time and preserves myocardial contractility and coronary vasodilatation during exercise. Ivabradine also protects the myocardium in acute ischemic conditions and has favorable anti remodelling properties in the long term. There is clinical proof of the antianginal and anti-ischemic effects of ivabradine instable angina. Pure heart rate reduction with chronic treatment with ivabradine is therefore of clear clinical benefit in patients with chronic ischemic disease.

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