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Late Sodium Current And I_f Inhibition: Targets of New Antianginal Drugs

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Abstract:

Ischaemic heart disease is the common cause of mortality and morbidity in developed countries despite tremendous development in treatment in last two decades. Recently cardiac Ion Channels and other cellular components have become the target of research for new cardiovascular drugs. A number of new drugs have emerged after pre-clinical and clinical trials. Ranolazine by inhibiting late sodium current in ventricular cardiomyocytes and ibavradine by inhibiting I_f current in pacemaker cells have emerged as effective new antianginal drugs. Both are discussed in this review article.

Key Words: Late Sodium current (I*PNa*), Diastolic tension, After depolarization, I*f* current, heart rate.

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RANOLAZINE

Introduction:

The late sodium current during the plateau phase of cardiac ventricular action potential has become a new target of cardiovascular drugs[1]. Ranolazine, a new drug by inhibiting the late sodium current has emerged as a cardio-protective drug during pathological conditions like myocardial ischemia, hypertrophy, hypoxia, ischemia / reperfusions and heart failure[2].

Discussion:

Late sodium current (also called as late I*Na* or I*PNa*) in cardiomyocyte a new concept proved and confirmed experimentally by patch-clamp recordings of single sodium channel and whole cell recording[1]. Activation of voltage gated (Tetrodotoxin sensitive) sodium channels forms the upstroke (phase 0) of the ventricular action potential[1]. During this phase 0 (depolarization) tremendous amount of sodium ions enter into the cell through these sodium channels creating an inward sodium current (I*Na*). This current (I*Na*) lasts for only a few milliseconds before sodium channels inactivate. Conformational change then occurs in each channel from inactivated state to a resting closed state (i.e. recovery) during repolarization[2]. Most of the sodium channels are inactivated within a few milliseconds and remain closed and non-conducting throughout the plateau phase (phase 2) of the cardiac action potential[1,2].

However, a small percentage of sodium channels either do not close or close and then reopen. They continue to open and close spontaneously during the plateau phase. The late opening of these channels allows a sustained current of sodium ions to enter into myocardial cells throughout the systole. This current is called late, sustained or persistent inward sodium current (I*PNa*) to distinguish it from the peak or transient sodium current in phase 0[1,2]. Though this current (I*PNa*) is very small (1% of peak I*Na*) but it lasts 50-100 times longer and continues to flow throughout the plateau phase in ventricular cells as well as in Purkinje fibers and is sufficient to prolong the action potential duration (APD)[1,2].

It appears that intracellular sodium rises in two phases during the action potential. One is an in-tense phase lasting for a few milliseconds during the phase 0 (upstroke) of the action potential another is a weak phase lasting hundreds of milliseconds during phase 2 (plateau)[1]. In both phases intracellular sodium loading is almost equal[1]. Blocking the late component of the sodium current (late *INa*) can reduce sodium loading by about 50%[1]. Late I_{Na} increased during hypoxia and heart failure and causes repolarization failure, prolong APD and early after depolarization (EAD), and arrhythmia[1,2]. Blocking I*PNa* with tetrodotoxin has shown to reduce action potential duration (APD) and abolished EAD[1,2]. Experimental studies also showed that EAD can be induced by increasing I*PNa*[1,4]. So the I*PNa* is one of the factors that can predispose cardiac cells to failure of repolarization and the initiation of early afterdepolarization and re-entrant arrhythmia[1,2].

Ion channels are not uniformly distributed throughout the ventricle[1]. Heterogeneous distribution of ion channels causes transmural heterogeneity of the magnitude of late I*Na* and thus of APD which may trigger ventricular tachyarrhythmia such as torsade de pointes[1,5].

Several other pathological conditions and disease states can significantly increase the late component of the sodium channel current such as long QT-3 syndrome (mutant sodium channel gene SCN5A), hypoxia, heart failure and post myocardial infarction[1,6]. The amplitude of late I*Na* is reported to be increased 2-4 folds from during normoxia to during hypoxia[2].

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Besides sodium channel there exists sodium-calcium exchanger (NCX) in the cardiac cell membrane[2]. When intracellular sodium ion concentration increases through late I*Na* there is an increased exchange of intracellular sodium for extra cellular calcium through NCX activation[2].

As cardiac function is dependent on homeostasis of the intracellular concentrations of sodium [Na]i and calcium [Ca]i pathological conditions, such as ischemia and heart failure are often associated with disruption of these ionic homeostasis and subsequent mechanical and electrical dysfunction[1,2]. The first step is the rise in intracellular sodium concentration which may be followed by increase in sodium-calcium exchange with cellular uptake of calcium and excessive calcium loading of the sarcoplasmic reticulam[2]. Calcium overloading is associated with increased diastolic wall tension and reduced systolic force generation, an increase in oxygen consumption and electrical instability. Increased diastolic wall tension causes intramyocardial vascular compression that reduces blood flow and oxygen supply to myocardium[2]. In addition calcium overload may lead to cell injury and death if not corrected[2].

An immediate consequence of increased late sodium current (I_{Na}) is the development of EAD. Long-term consequences of sodium loading leads to calcium loading and late after-depolarization. When sodium loading exceeds 12-15 m mol/ l (i.e. three times normal sodium concentration) the rise in calcium triggers repetitive release of calcium from srcoplasmic reticulum[1]. This process is a pathological version of the calcium induced calcium release process, which is part of normal excitation-contraction coupling[1]. This oscillatory calcium release may precipitate arrhythmia. Each oscillation of calcium activates the sodium-calcium exchanger which is electrgenic (three sodium ions are exchanged for each calcium ion) by creating inward sodium current through NCX and may cause late afterdepolarization[1,2]. If this current is large enough it can trigger additional action potential and so form a mechanism for arrhythmia based on ectopic beating[1,2].

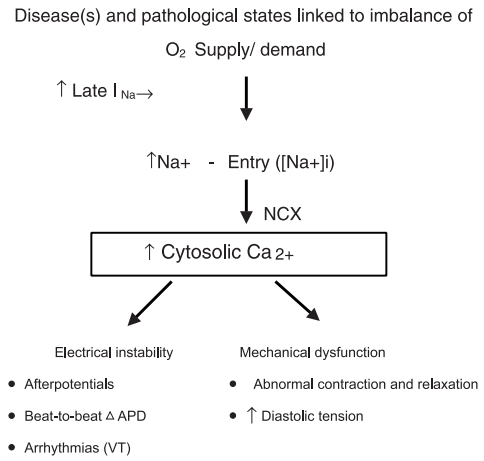

Fig.1: Increase in intracellular sodium concentration ([Na+]i) in pathological conditions linked to imbalances between oxygen supply and demand causes calcium entry through the Na+/Ca+2 exchanger (NCX). A pathologically enhanced late sodium current (I_{Na}) contributes to [Na+]i-dependent calcium overload, leading to electrical instability and mechanical dysfunction. APD, action potential duration; VT, ventricular tachycardia (Reproduced with permission from ref. 2).

A large number of clinical data showed that ischemia impairs LV relaxation, reduces diastolic compliance and increases regional myocardial stiffness[2]. Thus it appears that LV diastolic function is impaired during episodes of myocardial ischemia (angina pectoris). Ranolazine, a piperazine derivative improves both LV diastolic function and reduce the severity of angina by inhibiting late I*Na*[2,3]. Ranolazine is a selective blocker of late I_{Na} at concentrations < 10ìmol[2]. Though the exact mechanism of late I*Na* inhibition is unknown.

Three well known clinical studies showed that ranolazine significantly improves exercise performance, reduces the frequency of anginal attacks and consumption of nitroglycerin and delays signs and symptoms of ischemia without significantly affecting the haemodynamic parameters such as heart rate or blood pressure[7,8]. In MARISA trial (Monotherapy Assessment of Ranolazine in Stable Angina) sustained release ranolazine at doses from 500mg to 1500mg twice daily showed significant improvement in exercise performance and delays occurrence of symptoms and signs of ischemia without significant haemodynamic effects[9]. In CARISA trial (Combination Assessment of Ranolazine in Stable Angina) sustained release ranolazine (750mg or1000mg bid) were used in combination with diltiazem, amlodipine or atenolol in patients with chronic stable angina[10]. Results showed that sustained release ranolazine offers additional anti-anginal effect and anti-ischemic efficacy in patients receiving standard doses of anti-ischemic agents such as atenolol, diltiazem, or amlodipine without significant changes at rest or during exercise[9,10]. In ERICA trial (Evaluation of Ranolazine in Chronic Angina) ranolazine was used at a dose of 500mg b.i.d. vs. placebo for a week, and then titrated to 1000mg b.i.d. for 6 weeks. The results showed a significant reduction in anginal attacks, with excellent tolerability, without syncope or torsade de pointes[9,10]. MERLIN TIMI 36 (Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST segment elevation with acute coronary syndrome) TIMI (Thrombolysis in Myocardial Infarction) the largest clinical trial with

ranolazine which included 6560 patients with acute coronary syndrome, the results of which has been published recently[11]. Besides its efficacy in reducing cardiovascular death and recurrent ischemic events, ranolazine also showed anti-arrhythmic efficacy[11,12].

Conclusion:

Ranolazine reduce anginal symptoms by blocking intracellular sodium and calcium overload in myocardial ischemia through selective inhibition of late I_{Na}. Ranolazine has consistently demonstrated its anti-ischemic properties and has been shown to prolong exercise duration and time to occurrence of ischemia without significantly affecting haemodynamic parameters such as heart rate and blood pressure[12]. It is well tolerated in short and long term use with only minor QTc prolongation[9]. In addition it has excellent safety profile at all the currently tested doses[12,13]. In chronic angina ranolazine has anti-anginal and anti-ischemic effects, improving exercise performance and decreasing angina frequency and nitrate use. In addition it has anti-arrhythmic effects[14]. Many patients with chronic stable angina are not suitable for definitive therapy with revascularization because of complicating factors such as age, medical co-morbidities and unsuitable coronary anatomy[15]. These patients remain symptomatic despite traditional anti-anginal medication such as beta-blockers, calcium channel blockers and nitrates. In this context Ranolazine remains the hope.

IVABRADINE

Introduction:

The total number of heartbeats in a lifetime remains fairly constant across species and there exists an inverse relationship between resting heart rate and life expectancy[1]. Epidemiological studies demonstrated that high resting heart rate is a strong predictor for total and cardiovascular mortality in healthy populations[2]. The association between resting heart rate and mortality has been observed in patients with hypertension, metabolic syndrome, in the elderly and in patients with stable coronary artery disease (CAD)[2]. Heart rate reduction is one of the important goals of treatment in angina. In patients with CAD a lower heart rate is associated with a more favorable prognosis[3]. Many experimental and clinical studies suggested that heart rate reduction may improve coronary endothelial function and atherosclerosis[2,3]. Jean CT et al[2]. reported that patients with CAD with a resting heart rate between 77 and 82 bpm had a significantly higher risk for total mortality and it was even greater if resting heart rate e" 83bpm. They are prone to more rehospitalizations for cardiovascular reasons, independently of major risk factors like diabetes, hypertension and dyslipidemia when compared with patients with a resting heart rate of d" 62bpm. Of the existing heart rate reducing agents â-blockers reduce heart rate effectively and is used as a first line therapy in stable angina in the absence of contraindications. However, their use is limited because of their negative inotropic effect and is restricted in patients with obstructive airway disease, peripheral artery disease and atrioventricular conduction disorders. Ivabradine a new drug by inhibiting the *If* current in sinus node reduce heart rate effectively and is devoid of limitations of â-blockers, has emerged as a new anti-anginal drug.

Discussion:

Ivabradine is a selective and specific inhibitor of *If* (funny) current. It lowers heart rate substantially by inhibiting the *If* channel in sinoatrial node (SAN)[4].

The pace-making activity is generated in many regions of the heart including the SAN, the AV node, the bundle of His, and the Purkinje fibers. However, because of its fastest intrinsic rhythm SAN determines the heart rate[5]. At resting membrane potential cells in the SAN are hyperpolarized. Then they generate a slow diastolic depolarization, driving the membrane potential towards a thresh-hold level and triggering the next action potential[5].

The slow diastolic depolarization of the pacemaker cells in the SAN is regulated by four ionic currents: the outward potassium current Iki, inward I*f* current, and two calcium currents I*Ca*- L (Long Lasting) and I*ca*- T (transient). The I*f* current is the intrinsic pacemaker current of the heart[5]. This is a mixed Na+/K+ current which is slowly activated on hyper-polarization and determines the rate of the slow diastolic depolarization and the time interval between successive action potentials and thereby controls heart rate[5].

The membrane ion channel *f* channel is responsible for the I*f* current in the SAN. It is a member of the hyper-polarization activated, cyclic nucleotide-gated (HCN) family of channels, exposed in the heart, the retina and the brain. There are four isoforms of the HCN channel (HCN1-4). HCN4 is the major component of the f channels in the heart[4,5].

Ivabradine and its active metabolite in the circulation S 18982 inhibit the I*f* current by binding to the HCN4 channels from the intracellular side of the cell membrane[6,7]. (Fig-2). I*f* current inhibition in the SAN prolongs the spontaneous slow diastolic depolarization of the pacemaker cells,

thereby increasing the time interval between action potentials and lowering heart rate. This is the primary mechanism of action of ivabradine[4,5].

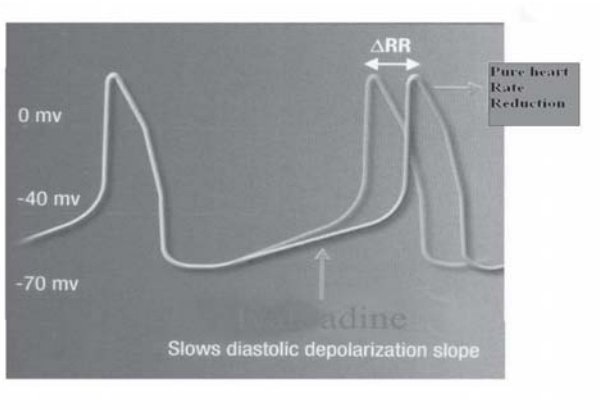

Fig.2: *Shows slowing of heart rate by ivabradine by slowing of diastolic depolarization slope through I_f inhibition (Reproduced with permission from ref.- 7).*

Ivabradine at concentrations of 1.5-3µm also inhibit retinal I*h* current through HCN1 which accounts for the visual symptoms reported with ivabradine[2,6].

Several randomized clinical trials studied with ivabradine comparing it with placebo or with active anti-anginal medications. The anti-ischaemic efficacy of ivabradine studied in 360 patients with stable angina and documented coronary artery disease[8]. Ivabradine produced dose-dependent reduction of heart rate at rest and exercise, which were associated with anti-ischaemic and anti- anginal effects during exercise tread mill testing. It also increases in time to ST-segment depression and angina. In another study[8] which included 386 patients with stable angina and documented coronary artery disease long time efficacy and safety were observed with ivabradine at 5 or 7.5 mg bid dose for 12 months. Both doses were effective in reducing heart rate and the number of anginal attacks and the drug was safe and well tolerated. In the both studies visual symptoms were reported and they resolved spontaneously. Ivabradine was compared with atenolol in the INITIATIVE (International trail on the treatment of angina with ivabradine vs. atenolol) study[6]. Ivabradine was found as effective as atenolol on exercise capacity in patients with stable angina. It was also compared with amlodipine and was shown to be as effective and safe as amlodipine[9]. Two large scale studies are now under way to see the efficacy of ivabradine in patients with coronary disease and heart failure. One is the ongoing large-scale BEAUTIFUL (morbidity-mortality evaluation of the I*f* inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction) study[10] and another is SHIFT (Systolic Heart Failure Treatment with I*f* inhibitor ivabradine) trial to see the prognostic value of heart rate reduction in patients with heart failure and the lack of intrinsic negative inotropic effects of ivabradine. These large scale clinical trials will help to determine the effects of ivabradine beyond heart rate reduction and angina in cardiovascular mortality and morbidity.

Concern about adverse cardiac effects as a consequence of I*f* inhibition with ivabradine have been studied. I*f* inhibition with ivabradine appears to be free of cardiac safety problems. The most frequent adverse events were bradycardia, ventricular extra-systoles and visual symptoms. Complete inhibition of I*f* channel at a higher concentration has been reported to lead to a 30-40% reduction in the heart rate[11]. At therapeutic dosage (5-7.5mg bid) it does not compromise myocardial contractility or haemodynamic parameters as a consequence of reduction of heart rate[11]. No significant electrophysiological adverse effect was observed except prolongation of sinus node recovery time (SNRT), sinoatrial conduction time (SACT) and the uncorrected QT interval, which have no clinical concerns[11,12]. Any drug that prolongs the heart rate would be expected to increase the QT interval. Ivabradine through reducing heart rate not has shown any significant effect on the QT interval and thus the risk of ventricular arrhythmia[10]. It does not affect atrioventricular conduction time (PR interval). Ivabradine showed also devoid of any intrinsic negative inotropic effect at rest or during exercise and in patients with global or regional impairment of LV systolic function[5,7]. Ivabradine also preserves mean coronary blood flow during exercise and decreases coronary vascular resistance during exercise which contrasts with the effects of â-blockers[6].

Conclusion:

In conclusion, ivabradine at therapeutic dosages by selective I*f* inhibition can reduce heart rate without compromising myocardial contractility or haemodynamic status or affecting the electrophysiological properties of the heart. It is an effective and safe anti-anginal agent, with anti-ischemic efficacy that appears non inferior to atenolol and amlodipine. It is a logical addition to the treatment of stable angina. Patients who are intolerant or have contraindication to beta blockers in whom symptoms are not controlled by previous antianginal medications might be the candidates of ivabradine.

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Ranolazine

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Ivabradine

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