Drug action(s), drug marketing, and clinical medicine. Suppression of ventricular arrhythmogenicity with If blockade in human heart failure: emerging clinical evidence for ivabradine treatment benefit beyond heart rate control

Mechanism(y) działania leku, strategia marketingowa producenta a medycyna kliniczna. Redukcja „automatycznej” arytmogenności komorowej przez hamowanie kanałów If w mięśniu lewej komory u pacjentów z niewydolnością serca: podstawy patofizjologiczne i pojawiające się dowody kliniczne na korzystne działanie iwabradyny poza kontrolą rytmu serca

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INTRODUCTION

Ivabradine has been continually marketed as “a pure heart rate lowering agent” (ditto) [1] whose “cardiac effects are specific to the sinus node” (ditto) [1]. A recent article in “Kardiologia Polska” [2] contributes importantly to the accumulating evidence that the cardiac effects of ivabradine are not only wider than specified by the manufacturer’s (simplified) marketing strategies but are also relevant to clinical cardiology [2]. This is not surprising because it is in agreement with a sizeable body of consistent animal data generated over the years and with reproducible studies in human myocardial tissue.

The role of marketing is to provide simple solutions to questions made look simple. Drug marketing, in the process of simplifying the acquisition and evaluation of new product information [3, 4], has a fundamental task to make the clinical answers and pharmacological solutions look simple. Today, drug marketing exerts a significant effect on the knowledge and awareness of physicians [3, 4]. Despite a number of clear downsides [3, 4], drug marketing is perceived as being associated with several advantages that, according to physicians, include easy exposure to new information, time saved on searching and accessing journal articles, easiness to remember the new information, and facilitated access to information on alternative pharmacological agents and strategies [3, 4].

The role of the physician is to treat diseases that are often complex. Reality, and biological reality in particular, proves often more complex than the marketing strategies would desire. Ivabradine exhibits its pharmacological action by inhibiting the If current [5], which, due to its function in the heart, is often labelled the ’pacemaker’ current [5]. In normal hearts, f-channels (HCN channels) are functionally expressed exclusively in the sinoatrial node cell membrane [5]. If is a mixed sodium and potassium current that is spontaneously activated at negative cell membrane potentials [5]. The flow of If causes spontaneous diastolic depolarisations and evokes spontaneous action potentials [5]. In the healthy heart, the treatment effect of ivabradine is indeed limited to the sinoatrial node because in the healthy heart the functional expression of f-channels is limited to the sinoatrial node cells [5].

There is robust evidence that myocardial disease alters the electrophysiological properties of the cardiac cells [6, 7]. In heart failure (HF) in man, one of the important disease-induced alterations is functional expression of the f-channels in the “ventricular” myocardium [6, 7]. This pathologic expression of If in human ventricular myocytes provides a basis [6, 7] for If-dependent spontaneous action potentials that may propagate in the ventricular myocardium [6, 8, 9]. Electrocardiography (ECG) manifestation of the If-driven ectopic electrical activity may involve (depending on local tissue con-
ditions and external stimuli such as adrenergic activation [6] isolated ventricular extrasystoles or runs of ventricular extrasystoles [10, 11].

In the era of powerful marketing-made-easy, clinicians (in contrast to investigators performing basic research in cardiology using human tissue [6, 7, 12] or animal models with gene transfer to mimic human disease [8, 9]) have remained largely unaware of the “ventricular” role of If in HF. Why is this “other” role of the If current in the human heart not generally known? The reasons seem to be several-fold and stems from the following: (1) pivotal clinical trials of ivabradine excluded subjects with high arrhythmogenic potential (history of ventricular tachycardia [VT] or implantable cardioverter-defibrillator [ICD], recent shocks) as fundamental exclusion criteria [13]; (2) neglect (in contrast to more recent trials in HF [14]) of arrhythmic death and/or aborted arrhythmic death as a registered study endpoint [13, 15]; (3) poor sensitivity to findings from large studies suggesting reduction of ventricular arrhythmogenicity with ivabradine [16]; and (4) lack, until today [2], of clinical studies designed to address the anti-arrhythmic effect of If inhibition in ventricular myocytes in human HF [6, 7, 10].

The above, taken together with the marketing drive for “simple” messages [3, 4], may explain why the anti-arrhythmic effect of If blockade in ventricular myocardium with ivabradine treatment in human HF has not made it to wide awareness of the clinical community.

IF-DEPENDENT VENTRICULAR ARRHYTHMOGENICITY: MECHANISMS AND EXPERIMENTAL EVIDENCE

Several lines of evidence indicate that in failing ventricular myocytes functional expression of the If current can (similar to the If physiologic action in the sinoatrial node) contribute to spontaneous diastolic depolarisations, spontaneous action potentials, and ventricular arrhythmogenicity. What in the sinoatrial node is manifested as a normal If-dependent spontaneous pacemaker activity, in diseased ventricular myocardium shows as ectopic electrical activity and ventricular arrhythmia in the form of isolated extrasystoles or runs of extrasystoles that, if fast enough, may constitute non-sustained VT or VT [10, 17]. Although there appear to be some differences in the if molecular basis and regulation in the sinoatrial node vs. ventricular myocardium [5–7, 10, 11, 18, 19], there is no doubt that in both locations If is highly responsive to adrenergic stimulation and is inhibited with ivabradine [5–7, 10]. In myopathic ventricular cells in human HF catecholamines shift the If activation threshold towards less negative potentials and thus the current becomes functional at typical diastolic potentials [6]. Beta-adrenergic stimulation also elevates the amplitude of If in pathologic ventricular myocytes [6], increasing the role of If-dependent ectopic electrical activity as an arrhythmogenic mechanism [6, 7, 10]. This is consistent with the well-known pro-arrhythmic effect of endogenous adrenergic stimulation in HF [11, 20] and the role of catecholamines as an established trigger of ventricular arrhythmia and sudden death in HF [20, 21].

If blockers (including ivabradine — the only If blocker in clinical use today) inhibit ventricular If-channels through the same mode of action as in the sinoatrial node cells [5, 6, 22].

Ventricular If contribution to the increased risk of malignant ventricular arrhythmias and sudden death through favouring spontaneous diastolic depolarisation in ventricular myocytes [22, 23], has been recently studied in a model of forced expression of If-channels in normal myocardium using somatic gene transfer [8]. These studies demonstrated that If-channels overexpression in undiseased ventricular myocytes, mimicking their spontaneous pathologic expression in HF, indeed leads to abnormal ventricular automaticity via If-dependent spontaneous depolarisations in the ventricular myocardium [8]. The abnormal, If-dependent electrical activity in the ventricular myocardium is enhanced by adrenergic stimulation [8, 10], and it is sensitive to pharmacological inhibition with ivabradine consistent with a direct, causal role of If [8].

It is important to realise that the pathologic, functional If expression in ventricular myocytes [6, 7, 12] leading to abnormal automaticity is just one of several mechanisms that promote ventricular arrhythmia in HF; others include delayed afterdepolarisations and re-entry [11, 20, 21]. However, mapping experiments have demonstrated that ventricular arrhythmias in HF are mainly due to nonreentrant mechanisms [21], an effect consistent with a role of If-dependent abnormal automaticity causing ectopic electrical activity [8, 11].

CLINICAL RELEVANCE OF VENTRICULAR ARRHYTHMOGENICITY SUPPRESSION WITH IF BLOCKADE: LINES OF PRIOR EVIDENCE IN HEART FAILURE PATIENTS

The pivotal SHiFT study of ivabradine in human HF randomised 6558 patients with chronic HF on guideline-based optimised HF therapy (ACE inhibitor and/or ARB in 93% and beta-blocker at maximally-tolerated dose in 93%) [13] to ivabradine vs. placebo. SHiFT was incapable of any direct evaluation of the anti-arrhythmic effect of “ventricular” If-blockade for two fundamental reasons. First, arrhythmic death, unfortunately, was not an endpoint in SHiFT [13] and because it was not evaluated, SHiFT reports do not include any specific data on arrhythmic death [13]. Secondly, history of any VT (unless a cardioverter-defibrillator, ICD, was already implanted) or — in those with ICD — ICD shock within six months prior to randomisation, formed exclusion criteria in SHiFT [13]. Despite these limitations, SHiFT has provided several lines of indirect evidence that the If blocking effect of ivabradine in the ventricular myocardium might be clinically relevant even in the lower-risk HF population. Not only was
the primary (combined) endpoint of cardiovascular death or hospitalisation for worsening HF reduced by ivabradine (24% vs. 29%, p < 0.0001 [13], but also ivabradine significantly reduced cardiovascular deaths (16% vs. 22%, p = 0.048 [15]) and deaths from HF (4% vs. 8%, p = 0.019 [15]). Since malignant ventricular arrhythmia is one of the principal mechanisms of death in HF [20, 24], the reduction in HF death and overall cardiovascular death with ivabradine treatment in SHIIT is likely to have occurred in part due to reduction in arrhythmic death.

The significant bias in SHIIT towards the lower-risk HF patient population (exclusion of patients with VT or ICD shock within six months prior to randomisation [13]) a priori minimised the potential of SHIIT to detect the benefit of malignant ventricular arrhythmia suppression occurring through “ventricular” If inhibition with ivabradine. Nevertheless, ECG Holter recordings in SHIIT (albeit limited to a small fraction of the SHIIT population and limited to 24 h on a single occasion at baseline and 24 h on a single occasion at eight months) clearly suggested a reduction in non-sustained VT with ivabradine (10% on ivabradine vs. 15% on placebo; absolute risk reduction by 5% and relative risk reduction by 33%) [15]. It is widely appreciated that while 24-h Holter recordings provide relatively reliable information on overall heart rate control (the focus of ivabradine vs. placebo investigation in SHIIT Holter substudy [15, 16]), this (short) recording duration is insufficient to determine rare arrhythmic episodes [25] due to a profound mismatch between the life-threatening ventricular arrhythmia prevalence (risk) vs. recording duration of only 24 h. Regrettably, 24-h ECG Holter recordings were obtained only in 501 out of 6558 patients in SHIIT (7.6%), resulting in the Holter analysis being underpowered for life-threatening ventricular arrhythmias and thus lacking the “statistical significance” of the anti-arrhythmic effect of ivabradine in HF [15]. In consequence, the 1/3 reduction in non-sustained VT with ivabradine in the SHIIT Holter substudy, although reported [15], has passed largely unnoticed.

**IVABRADINE ATTENUATION OF VENTRICULAR ARRHYTHMIA IN DECOMPENSATED HEART FAILURE WITH BACKGROUND ADRENERGIC STIMULATION: NOVEL CLINICAL DATA**

Sympathetic stimulation is a well-known, clinically-relevant trigger of ventricular arrhythmias in HF (including life-threatening ones) [20, 21]. At the same time, catecholamines potently stimulate the If current in the ventricular myocardium in human HF by reducing its activation threshold and increasing the amplitude of the current in human failing cardiomyocytes [6, 7]. Ventricular ectopic beats in patients with HF are an important risk factor for VT and arrhythmic death [26].

New clinical research data from the study on ‘Effects of ivabradine and beta-blocker therapy on dobutamine-induced ventricular arrhythmias in heart failure’ [2] indicate suppression of ventricular arrhythmogenicity in decompensated HF with ivabradine treatment in the presence of background adrenergic stimulation of increasing intensity. Using a clinically-relevant study protocol, Mert et al. [2] effectively overcame the challenging logistics and randomised 58 patients with decompensated HF and left ventricular ejection fraction < 35% requiring pharmacologic inotropic support to ivabradine vs. placebo (1:1). Continuous ECG recordings were performed at baseline, on ivabradine vs. placebo prior to dobutamine administration, and then at increasing doses of dobutamine with ivabradine or placebo on board [2]. Ventricular arrhythmogenicity was compared with that in a non-randomised group of similar patients on beta-blocker, subjected to increasing doses of dobutamine according to a similar protocol. The present findings [2] suggest a reduction in ventricular ectopic beats with ivabradine by ≈40% at the low and moderate dobutamine dose. Unsurprisingly, the high dobutamine dose was able to overcome the antiarrhythmic effect of ivabradine, presumably due to the magnitude of concurrent recruitment of ventricular arrhythmia mechanisms other than If-dependent enhanced automaticity. Because the majority of patients on ivabradine today are also on a beta-blocker [13], a clearly missing ‘natural’ study group in this work [2] is that of a combined ivabradine plus beta-blocker. Thus, it remains to be elucidated whether the anti-arrhythmic effect of ivabradine is additive to the anti-arrhythmic effect of beta-blockade. Importantly, the emerging technical ability to monitor heart rate continuously in a non-invasive manner [27] may overcome the shortcomings of ECG Holter recordings limited to 6-h intervals [2] or single-occasion 24 h [14, 15, 25]. The new technology [27] will conveniently enable long-term evaluation of the clinical significance of ventricular arrhythmia attenuation with ivabradine in human HF.

**CONCLUSIONS**

In conclusion, evidence in human cardiac tissue from failing hearts explanted at heart transplantation and in experimental models of human disease [6–11, 17, 22] shows consistently that If activation in ventricular myocardium may enhance ectopic electrical activity and promote arrhythmogenesis in HF [17, 22]; an effect particularly significant in the presence of background adrenergic stimulation [6, 7, 16].

The popular assumption that the action of If inhibitors is limited to the sinoatrial node [1] is true for the healthy heart [5, 22] because in the healthy heart f-channels are functionally expressed only in sinoatrial node cells. In myocardial disease, and in HF in particular, the f-channels undergo a pathologic, functional expression in the ventricular myocardium [6, 7, 12, 23]. By favouring spontaneous diastolic depolarisation in ventricular myocytes, the If current in human failing cardiomyocytes may contribute to the increased risk of malignant ventricular arrhythmias and death in patients with HF [6–10]. Prior work demonstrated that ventricular If is responsive to
blockade with ivabradine [8, 10]. With a smart clinical study design leading to novel findings, Mert et al. [2] indicate today an anti-arrhythmic effect of “ventricular” If blockade with ivabradine leading to reduction in ventricular arrhythmias in the presence of background adrenergic stimulation in human HF. This work [2] opens a new clinical research avenue and it should encourage further studies of the relevance of “ventricular” If blockade in the field of research that remains continuously active [9, 22, 23, 28–31] due to the fundamental clinical implications for HF patients.

Conflict of interest: none declared

References
