

If current inhibition and mortality reduction in heart failure: more than just a ‘pure’ effect of lowering heart rate

Blokowanie kanałów f a redukcja śmiertelności w niewydolności serca: więcej niż „czysty” efekt obniżenia częstości rytmu serca

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IF IN THE HEALTHY HEART: SINOATRIAL NODE-LIMITED F-CHANNEL EXPRESSION AND ‘PURE’ HEART RATE REGULATION

Cardiac pacemaking is a basic process in health and disease. The *If* current (often called ‘funny’ due to its many unusual properties) is an inward mixed Na⁺ and K⁺ current which is activated at negative cell membrane potentials (hence hyperpolarisation-activated) but whose activation causes spontaneous diastolic depolarisation [1]. These *If* properties are suited to the generation of repetitive electrical activity and the modulation of spontaneous rate [1]. Indeed, the degree of activation of the funny current determines the steepness of spontaneous depolarisation and thus the frequency of spontaneous firing in sino-atrial node (SAN) cells [1]. Because *If* is controlled by intracellular cAMP and thus is regulated by beta-adrenergic and muscarinic receptor agonists, it mediates the autonomic regulation of heart rate (HR) [1]. Furthermore, independent of autonomic modulation [2, 3], *If* is regulated by nitric oxide (NO) [4] through an intracellular pathway that involves cGMP and mobilisation of intracellular calcium [5]. The inhibition of endogenous NO production is associated with a reduction in HR both *in vitro* [6] and *in vivo* [2, 7], indicating that endogenous NO exerts a tonic positive chronotropic effect [2, 6]. Because of the many unusual features of *If*, it had been queried whether such a large body of properties could correspond to one single current. This was until the *If* molecular basis became clear with cloning the *f*-channels [8], which confirmed a unique structural basis for this specific membrane current [9]. Under normal physiological conditions, *If* is functionally expressed exclusively in the SAN cells [1].

Thus the principal publication from SHIFT (Systolic Heart Failure Treatment with the *If* Inhibitor Ivabradine Trial) in Lancet in 2010 rightly states that: “[beyond *If* inhibition in

SAN] in *healthy* hearts (...) ivabradine has no action on other channels in the heart or vascular system” [9].

HUMAN HEART FAILURE: IF IS FUNCTIONALLY EXPRESSED IN VENTRICULAR MYOCYTES

If is functionally inactive in normal (undiseased) ventricles, both because of very low expression of *f*-channels in the cardiomyocyte membrane and because of too negative, unphysiological voltage range of *If* activation [1, 10]. Marked upregulation of *If* expression in the ventricular myocardium, however, has been reproducibly documented in several animal models of heart failure (HF) and in humans suffering from HF in systematic studies of left ventricular (LV) myocytes sampled during cardiac surgery in HF patients [1, 10–12]. Moreover, in myopathic ventricular cells, in the presence of catecholamines, the *If* activation threshold is shifted towards less negative potentials and thus the current becomes functional at normal diastolic potentials [11, 13]. In ventricular myocytes, an *If*-dependent diastolic depolarisation may lead to generation of a propagated action potential — similar to the role played by *If* in SAN [13]. By favouring spontaneous diastolic depolarisation in myopathic cells, *If*-generated ectopic ‘pacemaker-like’ action potentials in the ventricular myocardium provide a mechanism of ventricular arrhythmia [10, 11] and arrhythmic death in HF [12, 13].

Thus, in HF the *If* channel is up-regulated in human ventricular myocardium through its amplified expression [14]. Moreover, in human HF this current also becomes functional at normal potential range and may generate spontaneous diastolic depolarisation in diseased ventricular myocytes, similar to its physiological role in the SAN cells [11–15]. *If* overexpression and its altered regulation in failing cardiac myocytes (causing, as documented in humans, functional

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availability of this current in the ventricular myocardium) represents an arrhythmogenic mechanism in HF [1, 11–15].

HEART FAILURE IS ASSOCIATED WITH AN INCREASE IN *I_f* STIMULANTS

Not only is *I_f* functionally expressed in failing LV myocytes [11–15] but also HF is associated with an increase in known *I_f* stimulants. Activation of the adrenergic nervous system [16] and increased myocardial NO production [17] are the hallmarks of HF. LV gene expression of constitutive NO synthase increases with the extent of LV dysfunction and the protein level of both (i.e. constitutive and inducible) NO synthases is increased in the failing myocardium [17]. Elevated expression of cardiac inducible NO synthase, as seen in patients with severe HF, attenuates responsiveness to beta-adrenergic stimulation [18], and there is ongoing research into the complexities of NO-dependent molecular mechanisms in HF [19].

To some surprise, in ventricular myocytes in a spontaneously hypertensive rat model, NO donors or NO synthase inhibition did not alter the amplitude or voltage dependence of *I_f* activation [20]. Nevertheless, the rat (in contrast to some other mammalian species) is not an optimal model of human cardiac disease [21] due to several important differences in cardiac myocyte electrophysiology [21–23]. Therefore continued study of human [21, 24] myocardial cells, as in the case of *I_f* expression and activation characteristics [10, 11, 14, 15], is of paramount importance in clinical reference to human cardiac pathophysiology [21].

The increased adrenergic tone in HF is associated, at the SAN level, with HR elevation [25] whereas at the level of the ventricular myocardium, catecholamines are an established trigger of ventricular arrhythmia [16, 26]. Indeed, sympathetic activation in HF has a profound arrhythmogenic impact [27], and evidence indicates that part of this impact may occur via ventricular myopathic cardiocyte *I_f* stimulation [11–15].

I_f-DEPENDENT PATHOLOGICAL ELECTRIC ACTIVITY IN VENTRICULAR MYOCYTES IS ABOLISHED BY *I_f* BLOCKADE

Patch-clamping experiments in failing human ventricular myocytes have revealed that the *I_f* current characteristics are consistent with feasibility of its activation in the failing ventricular myocardium and that this effect, as expected, is further promoted by *I_f* stimulants [11–15]. The *I_f* current blockers (including ivabradine) inhibit the ventricular *I_f* channels similar to their mode of action in SAN cells [1].

Ventricular *I_f* contribution to the increased risk of malignant ventricular arrhythmias and sudden death in patients with HF, through favouring spontaneous diastolic depolarisation in ventricular myocytes [1, 12, 13], has been recently mimicked by experimental, forced ectopic expression of *I_f* in a normal myocardium using somatic gene transfer (recombinant adenovirus gene carrier) of the ‘pacemaker’ *f*-channels [28]. Such forced *I_f* overexpression in undiseased ventricular

myocytes leads to abnormal ventricular automaticity (via spontaneous gradual phase 4 depolarisation that is normally typical of SAN cells) [28]. This abnormal electric activity is enhanced by adrenergic stimulation [28, 29] and is sensitive to pharmacologic inhibition with ivabradine, consistent with a direct, causal role of *I_f* [28]. Indeed, *I_f* blockers, including ivabradine, have been demonstrated to inhibit ventricular arrhythmias that occur when normal ventricular myocardium is overexpressed with *f*-channels [28, 29], mimicking the effect seen with enhanced *I_f* expression and its facilitated activation in the ventricular myocardium in HF.

SHIFT DEMONSTRATES REDUCTION OF HEART FAILURE-RELATED MORTALITY WITH *I_f* INHIBITION

In the recent SHIfT study [9], 6,505 patients with chronic HF were randomised to treatment with the *I_f* inhibitor ivabradine or a placebo on top of what was considered standard medical therapy. This study demonstrated that, over a median period of 22.9 months, ivabradine treatment was associated with a significant reduction of the combined endpoint of cardiovascular death or hospital admission for worsening HF (24% vs. 29%, $p < 0.0001$, primary endpoint of the study) [9]. *I_f* inhibition with ivabradine was also associated with a significant reduction of death from HF (3% vs. 5%, $p = 0.014$, pre-specified secondary endpoint) [9], bringing new focus to the clinical relevance of *I_f* modulation in disease states.

Because of the role in normal cardiac electrophysiology, *I_f* (and *I_f* inhibition) have been commonly associated exclusively with the SAN [9, 30–34]. Thus, analyses of the cardiovascular outcomes in SHIfT have been focused on the magnitude of HR reduction and suggested (unsurprisingly) that the treatment effect of ivabradine was accounted for by HR reduction [30–33]. As recently found, the therapeutic effect of *I_f* blockade in HF was particularly pronounced in patients with baseline HR ≥ 75 bpm (cutoff indicated by the European Medicines Agency) [33] as in this patient group ivabradine reduced also all-cause mortality (hazard ratio 0.83, 95% CI 0.72–0.96, $p = 0.011$) and cardiovascular mortality (hazard ratio 0.83, 95% CI 0.71–0.97, $p = 0.012$) [33].

Important beneficial mechanisms related to HR reduction in HF patients (and also in those with coronary artery disease) and the wider implications of SHIfT have been discussed in detail elsewhere [31–35].

LOWERING HEART RATE: A NON-EXCLUSIVE MECHANISM OF MORTALITY REDUCTION WITH *I_f* INHIBITION IN HEART FAILURE

Could part of the mortality reduction benefit seen in HF with ivabradine treatment in SHIfT result from inhibition of the ‘pacemaker’ current *I_f* that is known to be functionally expressed [11–15] in the myopathic ventricular myocytes?

Arrhythmic death, unfortunately, was not a pre-specified endpoint in SHIfT [9] and, as it was not evaluated, SHIfT re-

ports do not include any specific data on arrhythmic death [9]. Therefore there is no level 1 evidence for a clinically-relevant role of ivabradine occurring through inhibition of the abnormal *I_f*-dependent spontaneous electric activity in the ventricular myocytes. While it would be theoretically possible (though, given the current guidelines [34, 35], ethically difficult) to design a placebo-controlled arrhythmic death-focused study with *I_f* blockade in HF, execution of such a study is highly unlikely also because reliable documentation of arrhythmic death as the study endpoint would require continuous, telemetric ECG monitoring in all study subjects (with the population size and follow-up period exceeding that of SHIfT).

Malignant ventricular arrhythmia such as ventricular tachycardia (VT) or ventricular fibrillation is one of the principal mechanisms of death in HF [36, 37]. The presence of non-sustained VT on 24 h continuous ECG recording increases the odds of dying about three-fold over a 1–2 year follow-up period [36], and ventricular arrhythmia is a documented trigger event in the development of fatal arrhythmia [38]. Unfortunately, history of VT (unless a cardioverter-defibrillator, ICD, was already implanted) or, in those with ICD-ICD shock within six months prior to randomisation, were exclusion criteria from participation in SHIfT [9], minimising a priori the potential of SHIfT to detect the benefit of malignant ventricular arrhythmia suppression occurring through ‘ventricular’ *I_f* inhibition with ivabradine. Despite this important limitation, SHIfT still demonstrated a mortality benefit [9, 33], part of which is likely to arise from the action of ivabradine in diseased ventricular myocardium.

Heart failure death was a pre-specified endpoint in SHIfT, and it is well-known that lethal arrhythmias do occur in association with HF worsening [36, 37]. There is evidence that in HF exacerbation [9], a significant proportion of ‘pump failure’ deaths do overlap with arrhythmic deaths [36]; thus it is often impossible to clearly distinguish one mode of death from the other [36]. One should also take into account that the failing heart undergoes complex electrical remodelling of ventricular myocytes [39], and functional *I_f* expression in ventricular myocytes [10, 11, 14, 15] is one of several mechanisms that promote ventricular arrhythmia. Mapping experiments have demonstrated that ventricular arrhythmias in HF are mainly due to non-reentrant mechanisms [38]; an effect consistent with a role of *I_f*-dependent abnormal automaticity [12, 13, 15].

Suppression of *I_f*-dependent spontaneous abnormal electrical activity in the diseased LV achieved via *I_f* inhibition — leading to the mortality reduction with ivabradine in HF — is an alluring hypothesis that is supported by several lines of patho- and electrophysiological evidence. These lines of evidence include (i) documented functional expression of *I_f* in ventricular myocytes in human HF [10, 11, 14, 15], (ii) an HF-associated increase in *I_f* stimulants such as the adrenergic drive and myocardial NO production [16–19, 26–27], and (iii) documented ivabradine suppression of abnormal electrical activity associated with *I_f* overexpression in the ventricular myocardium [28, 29].

Although analysis of the cardiovascular outcomes in SHIfT [9] has suggested that the treatment effect of ivabradine in HF is accounted for by HR reduction [9, 29], the degree of HR reduction with ivabradine is likely to reflect the degree of *I_f* inhibition not only in the SAN but also the degree of *f*-channel inhibition in the ventricular myocardium. Thus the widely documented association of the magnitude of clinical benefit of *I_f* inhibition with the degree of HR reduction in HF [30–33, 35] is not in any conflict with the contributory effect of *I_f* inhibition in ventricular myocytes that leads to malignant automaticity suppression (i.e. the more effective, or the better response to, *I_f* inhibition in terms of heart rate reduction magnitude, the more effective is the inhibition of the pathologically expressed *I_f* in the myopathic ventricular cells).

In HF, increased HR is a marker of increased sympathetic activation [25, 40, 41], and increased sympathetic activation stimulates malignant ventricular arrhythmias [16, 26] while the functional expression of *I_f* in the myopathic ventricular myocytes provides an important arrhythmic mechanism [11–15] that is sensitive to adrenergic stimulation [12–15]. The relative contribution of the two mechanisms (i.e. HR reduction as a result of ivabradine action in the SAN and malignant arrhythmia suppression as a result of ivabradine action in the ventricular myocardium) to the observed mortality reduction [9, 33] is impossible to dissociate because pharmacologic *I_f* blockers inhibit *I_f* both in the SAN and likewise in the failing ventricular myocytes [1, 10, 11, 14, 15, 29]. Thus the HR reduction seen with ivabradine in HF may be, to an extent, an epiphenomenon of the ‘ventricular’ *I_f* inhibition that (also) occurs with ivabradine treatment. For this reason, it is not surprising that (i) in SHIfT patients with baseline HR ≥ 75 bpm (an index of increased sympathetic drive) [25, 40, 41], ivabradine significantly reduced not only HF-related death (hazard ratio 0.61, 95% CI 0.46–0.81, $p < 0.001$) but also all-cause mortality (hazard ratio 0.83, 95% CI 0.72–0.96, $p = 0.011$) and cardiovascular mortality (hazard ratio 0.83, 95% CI 0.71–0.97, $p = 0.012$) [33], and (ii) that the primary determinant of study outcomes was, as shown recently, the magnitude of HR reduction by ivabradine combined with beta-blocker, and not the background beta-blocker dose [42].

When taken together, the evidence indicates clearly that part of the therapeutic effect of ivabradine in HF may be associated with the inhibition of the ‘pacemaker’ current *I_f* in the diseased ventricular myocytes. Interestingly, a functional role of the pathological *I_f* expression in ventricular myocytes has been proposed [2, 4, 43] following the discovery of a novel *I_f*-dependent signalling pathway in the SAN cells [2–4]. Fifteen years later, an overlooked [9] mechanism [1, 11–15] would undoubtedly benefit from its further elucidation in the context of novel data [9, 34] that is consistent with a clinical relevance of *I_f* that extends beyond heart beat generation and HR regulation.

CONCLUSIONS

While the popular assumption that the action of *I_f* inhibitors is limited to the sino-atrial node [9, 34] is true for the healthy heart [1], several lines of evidence indicate that this assumption may not hold for the failing human heart [11, 15, 28, 29]. By favouring spontaneous diastolic depolarisation in ventricular myocytes, the *I_f* current (which is functionally absent in normal ventricular myocardium but is functionally expressed in human failing cardiomyocytes [11–15]), may contribute to the increased risk of malignant ventricular arrhythmias and death in patients with HF; an effect responsive to *I_f* blockade [28, 29]. Several lines of evidence indicate that part of the mortality reduction seen with ivabradine treatment in SHIFT [9, 33] may result from inhibition of the ‘pacemaker’ current *I_f* in the diseased ventricular myocytes. Thus, when it comes to mechanisms behind the recently demonstrated mortality reduction [9, 33] in HF patients treated with an *I_f* inhibitor, there is likely to be more than just a ‘pure’ heart rate-lowering effect of the *I_f* blockade!

Conflict of interest: none declared

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