Ivabradine: Heart Rate and Left Ventricular Function

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The classic paper discussed in this essay:

Manz M, Reuter M, Lauck G, Omran H, Jung W: A single intravenous dose of ivabradine, a novel I_f inhibitor, lowers heart rate but does not depress left ventricular function in patients with left ventricular dysfunction. *Cardiology* 2003;100:149–155.

Ten years ago, Manz et al. [1] published an article in *Cardiology* entitled ‘A single intravenous dose of ivabradine, a novel I_f inhibitor, lowers heart rate but does not depress left ventricular function in patients with left ventricular dysfunction’. Their work did neither present a mega-trial nor was it linked to any therapeutic achievement. On the contrary, it was a rather small, randomized, single-blind, placebo-controlled study in 43 patients. It set out to investigate the effects of intravenous ivabradine on echocardiographic indices of left ventricular (LV) systolic function in patients with regional LV dysfunction due to coronary artery disease (CAD) or global LV dysfunction due to cardiomyopathy. Only 38 patients completed the study according to the protocol (CAD patients: 15 ivabradine and 7 placebo; cardiomyopathy patients: 12 ivabradine and 4 placebo). Heart rate was reduced by $17.6 \pm 4.7\%$ with ivabradine versus $1.5 \pm 5.8\%$ with placebo. This reduction in heart rate was expected and was comparable to that previously reported both in healthy volunteers [2] and in patients with stable CAD [3], but this is not the main point of the study. The real highlight of the report is that the mean maximum decrease in LV ejection fraction (LVEF) was preserved with ivabradine [0.2 vs. 1.7% (placebo)], as were fractional shortening and stroke volume in both subgroups of patients studied. Moreover,

intravenous administration of ivabradine caused no serious adverse events, with only four mild adverse events possibly related to ivabradine, all of which resolved spontaneously on the same day.

Thus, Manz et al. [1] demonstrated that ivabradine is not just another reducer of heart rate. It is the only compound that can reduce heart rate without affecting any other hemodynamic parameter and without any undesirable effects. This is because ivabradine is different from other heart rate-reducing drugs (i.e. β -blockers or some calcium channel blockers), since it possesses two levels of selectivity. Ivabradine has anatomical selectivity for a few cells located in the sinus node of the right atrium [4], and so it does not act anywhere else in the body. This makes it very different from the β -blockers, which act wherever β -receptors are present (i.e. in the ventricles, causing negative inotropism, and in the bronchi, causing vasoconstriction) and from calcium channel blockers, which act on the calcium channels of the heart and smooth muscle causing negative inotropism, hypotension and constipation.

Ivabradine is also selective in the manner that it acts on the sinus node cell itself. Ivabradine is a selective and specific inhibitor of the myocardial I_f channel involved in pacemaking [5]. At therapeutic concentrations, both in

animals and humans, ivabradine does not affect any other cardiac channel or current (i.e. Na, K or Ca²⁺ currents), though its use is related to some inhibition of the I_h current in retinal hyperpolarization-activated cyclic nucleotide-gated channels, which leads to visual symptoms in 2–3% of patients [4, 6]. This highly specific mode of action explains the lack of an effect of ivabradine on myocardial contractility and other hemodynamic parameters, as has been repeatedly observed in animal studies [7–9], and on LV performance, as described by Manz et al. [1].

The way that ivabradine inhibits the I_f channel itself is also unique and deserves comment. To be active, ivabradine needs to penetrate channels that are hyperpolarization activated. When heart rate is high, the channels are hyperpolarized and their probability of being open is high: ivabradine penetrates the channel easily and reduces heart rate. When heart rate is low or in the physiological range (≤ 60 b.p.m.), the effect of ivabradine is at a therapeutic level minimal or nonexistent as more channels are closed, making penetration for ivabradine difficult [4]. This unique mechanism of action of ivabradine can be considered as a sort of safety valve against the usual side effects of all the other heart rate-reducing agents, i.e. severe bradycardia. It is, therefore, not at all surprising that Manz et al. [1] did not encounter bradycardia in any of their ivabradine-treated patients.

This early experience was pivotal for better defining the therapeutic properties of ivabradine. In 2008, 5 years after publication of the article by Manz and colleagues, De Ferrari et al. [10] assessed the effect of ivabradine infusion (0.1 mg/kg over 90 min) using 24-hour hemodynamic monitoring in 10 patients who were receiving β -blocker for severe heart failure (New York Heart Association class III, LVEF $21 \pm 7\%$). No serious adverse events occurred. One hour after the end of infusion, heart rate had reduced by 27% ($p < 0.01$) without decreasing cardiac index ($p = 0.15$; fig. 1). There were also significant increases in stroke volume (by 51%, $p < 0.01$) and work, with no increases in diastolic volumes or any apparent unfavorable hemodynamic consequences. Cardiac output also tended to increase.

When taken together, the data from Manz and De Ferrari support the rationale for intravenous use of ivabradine in patients with acute heart failure with elevated heart rate. Their data also predicted the findings of the echocardiographic substudy of SHIFT (Systolic Heart Failure Treatment with I_f Inhibitor Ivabradine Trial) [11], which showed that the administration of ivabradine to patients with systolic heart failure, low LVEF ($\leq 35\%$) and resting heart rate ≥ 70 b.p.m. brought about significant

reductions in end-systolic and end-diastolic volume indices, with a relative increase in LVEF, leading to reverse remodeling [12]. Similar (if not identical) data were obtained in the echo substudy of the BEAUTIFUL Trial (Morbidity-Mortality Evaluation of the I_f Inhibitor Ivabradine in Patients with Coronary Artery Disease and Left Ventricular Dysfunction) [13, 14] in patients with CAD and LV dysfunction (LVEF $\geq 40\%$), independently of baseline heart rate. This implies that heart rate reduction may have a beneficial effect on the myocardium in patients with impaired LV function or overt heart failure. This is in line with the hypothesis of ‘tachycardia-mediated cardiomyopathy’, by which chronic elevation in heart rate produces a reversible syndrome of LV dysfunction, as well as the observation that pacing at progressively increasing levels of heart rate worsens LV function and reduces exercise capacity [15, 16]. Heart rate-reducing agents like β -blockers, which improve outcome and LV function in heart failure [17], are also known to have additional effects on autonomic tone, contractility and arrhythmia, which could contribute to their benefit. The SHIFT data indicate that elevated heart rate is not simply a marker of poor LV function and outcome: it is also a modifiable risk factor in heart failure. Indeed, ivabradine improved outcome and LV function by reducing heart rate without any direct hemodynamic action, and the degree of benefit was related to the magnitude of heart rate reduction [11, 12, 18].

The question is: Why is heart rate reduction a positive inotropic intervention in heart failure? There are several possible explanations, two of which, at least, were influenced by the findings from Manz et al. [1]. First, in vitro studies of human myocardial papillary muscle indicate that the tension of nonfailing fibers increases proportionally to the increase in heart rate. By contrast, the tension developed by fibers from heart failure patients decreases in response to the same increase in heart rate. The force-frequency relationship is therefore lost in heart failure [19]. Consistent with this concept, in patients with cardiomyopathy, increasing heart rate by pacing actually decreases LVEF [20]. The study of De Ferrari et al. [10] is another in vivo demonstration of a negative force-frequency relationship in patients with advanced heart failure showing that the relationship can be beneficially reversed by ivabradine.

Second, the indirect positive inotropic effect of heart rate reduction by ivabradine in heart failure may not be restricted to the heart, but may also have an effect on the vascular system. It is known that aging and high heart rate cause changes in elastin fibers and arterial elasticity. Hu-

Fig. 1. Change in heart rate, stroke volume and cardiac index over 24 h in patients receiving an intravenous infusion of ivabradine for 3 h (x-axis not to scale). Adapted from De Ferrari et al. [10].

Fig. 2. Change in stroke volume and cardiac output over 8 months in patients with systolic heart failure participating in the SHIFT trial [22].

man aorta can experience up to a trillion stretch cycles during a lifetime, depending on basal heart rate. Therefore, even physiologically, there is a risk of undergoing structural changes leading to increased stiffness [21]. The idea is that the left ventricle and the aorta are closely integrated, since LVEF is a measure of ventricular-arterial (afterload) coupling. Interestingly, the effective arterial elastance, integrating the mean and pulsative load on the heart, directly depends on total peripheral resistance and heart rate [21]. It follows that heart rate reduction with ivabradine should reduce effective arterial elastance or, in clinical terms, afterload. Further data from SHIFT showed that heart rate reduction with ivabradine can directly affect the vascular system and that the reported reduction in afterload was mainly triggered by a decrease in vascular pulsatile load, whereas systemic resistance remained con-

stant [22]. A better arterial compliance appears to result in improved ventricular arterial coupling with a significant increase in LVEF and stroke volume, without changes in LV contractility and cardiac output (fig. 2) [22]. This is in line with the work of Manz et al. [1] and De Ferrari et al. [10], as well as the two remodeling substudies of SHIFT and BEAUTIFUL [12, 13]. These effects may contribute to the therapeutic action of ivabradine not only in heart failure, but also in effort angina, where ivabradine exerts therapeutic effects similar – if not superior – to those of β -blockers and/or calcium channel blockers, without exerting any negative inotropic action, and actually allowing the physiological increase in contraction induced by exercise [23]. The data of Manz et al. [1] also explain why, in ASSOCIATE (Evaluation of the Antianginal Efficacy and Safety of the Association of the I_f Current

Inhibitor Ivabradine with a Beta-Blocker) [24], treatment with ivabradine brought about further reduction in heart rate and improved exercise capacity in angina patients chronically treated with β -blockers.

There are other – more direct implications – of the article of Manz et al. [1] in *Cardiology*. The effect of intravenous administration of a bolus of 10–15 mg of ivabradine prior to coronary computed tomography (CT) angiography has been explored in a randomized double-blind study in 370 patients with known or suspected CAD and heart rate ≥ 70 b.p.m. Intravenous ivabradine was found to provide rapid, safe and sustained heart rate reduction [25]. Use of ivabradine in this setting would increase the number of patients who could benefit from coronary CT angiography. A randomized, placebo-controlled, blinded, clinical trial of intravenous ivabradine has also been performed in patients with acute coronary syndrome. VIVIFY (Evaluation of the Intravenous I_f Inhibitor Ivabradine after ST-Segment Elevation Myocardial Infarction) was set up to determine the effects of intravenous ivabradine in patients receiving primary percutaneous coronary intervention for ST-segment elevation myocardial infarction [26]. Intravenous ivabradine was reported to be safe and well tolerated. In terms of efficacy, it produced a rapid and sustained reduction in heart rate, and was associated with lower levels of biochemical marker release, lower LV volumes on echo-

cardiography and a smaller area of delayed hyperenhancement on magnetic resonance imaging.

In conclusion, the peculiar action of ivabradine described by Manz et al. [1] is actually the peculiarity of this drug. Ivabradine, by contrast to all the other main cardiovascular therapies, selectively targets a small number of cells, i.e. those of the sinoatrial node. Moreover, the action of ivabradine is use dependent, and heart rate is only reduced when it is elevated. Thus, ivabradine could be considered a precise drug with a specific and selected target – therapy with ivabradine therefore constitutes personalized medicine, similar to the situation with anticancer therapy. On the other hand, and in contrast to anticancer drugs, ivabradine has been proven to be beneficial in a broad range of manifestations of cardiovascular diseases, including angina, myocardial infarction and heart failure. This is hardly surprising since the physiological role of the few cells targeted by ivabradine relates to a fundamental property of the heart: that of beating to support life.

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