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Preclinical Results with I_f Current Inhibition by Ivabradine

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Abstract

Ivabradine, a highly selective I_f current inhibitor acting directly on the sinoatrial node, induces a rapid, sustained and dose-dependent reduction of heart rate at rest and during exercise, without significant effects on atrioventricular conduction, left ventricular (LV) contraction-relaxation or vascular tissues. These properties, associated with an improvement in LV loading related to bradycardia, resulted in an increase in stroke volume and preservation of cardiac output at rest and during exercise. Reducing myocardial oxygen consumption and improving oxygen supply, ivabradine reduced the severity of ischaemia and associated regional contractile dysfunction of the stunned myocardium. Long-term administration of ivabradine in rats with chronic heart failure improved cardiac haemodynamics associated with a progressive remodelling of LV structure. In dyslipidaemic mice, ivabradine prevented the renal and cerebrovascular endothelial dysfunction associated with atherosclerosis. These preclinical data suggest that long-term reduction in heart rate with ivabradine might interact with multiple *a priori* unexpected mechanisms involved in cardiac and vascular remodelling processes associated with chronic heart diseases.

For a long time, β-adrenoceptor antagonists (β-blockers) and non-dihydropyridine calcium channel blockers were the only therapeutic agents available for the treatment of symptomatic cardiac ischaemic diseases because they can rapidly restore the equilibrium of the balance between myocardial oxygen supply and demand of the ischaemic myocardium. As evidenced, reduction of heart rate and redistribution of regional blood flows are common and key determinants for such a beneficial effect. However, some associated properties of these drugs – such as their simultaneous reduction in myocardial inotropism and dromotropism, properties that are entirely inherent to their pharmacological mechanism of action – also limit their therapeutic usefulness in patients with altered basal contractile function and/or rhythmic disorders. Consequently, the development of original and new drugs that could selectively reduce heart rate, i.e. without concomitant negative effects on myocardial contractile force (inotropy), relaxation (lusitropy) and conduction (dromotropy), has been an extensive and difficult pharmacological challenge for the pharmaceutical industry over the last 20 years. Multiple compounds were successive candidates for this new class of drugs (e.g. ZD 7288, E 4080, UL-FS or zatebradine), but to date only the bencyclobutane derivative S 16257, ivabradine (Procoralan®, Corlentor®),[1] a highly selective I_f cur-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

rent inhibitor acting directly on the sinoatrial node, has completed clinical development and is now available in medical practice.

1. Pure Heart Rate Reduction

Using multiple *in vitro* preparations (rat right atria, rabbit sinus node preparations, isolated pacemaker sinus node cells, etc.), it has been clearly demonstrated that ivabradine decreases heart rate by reducing the slope of the slow diastolic depolarisation of pacemaker cells in a concentration-dependent manner without significant changes in the action potential amplitude and duration up to 3×10^{-6} mol/L.[1] Using the patch clamp technique, it was demonstrated that the ivabradine-induced decrease in heart rate was related to its ability to selectively reduce the amplitude of the inward hyperpolarising I_f current of these pacemaker cells without any interference with other ionic channels or receptors.[2,3] Ivabradine acts only when the I_f channel is open and the kinetics of inhibition of the pacemaker current is 'use dependent' (i.e. the intensity of the blockade increases with the number of firing pulses).[4] The molecular basis of this property has been demonstrated recently to occur at the level of the hyperpolarisation-activated cyclic nucleotide-gated channel 4 gene (HCN4) isoform of the I_f current, its predominant transcript in the human sinoatrial node.[5] This result explains the recent observation of sinus node bradycardia in members of a large family with a mutation in the gene coding for the pacemaker HCN4 ion channel.[6]

In vivo, ivabradine reduces heart rate in a dose-dependent manner and it is independent of the pathophysiological status, since this heart rate-slowing effect remains unchanged in animals or humans with reduced myocardial contractility or relaxation, such as in congestive heart failure. This heart rate reduction also remains effective after long-term administration via either intravenous or oral routes.[1] Because I_f channels are activated by a use-dependent mechanism, by hyperpolarisation and by direct binding of cyclic adenosine monophosphate (cAMP), the reduction in heart rate induced by ivabradine is more marked at higher than at lower heart rates. Surprisingly, this reduction is limited to 18–20% of basal heart rate, either at rest or during exercise in conscious animals[1,7] and in humans,[8] even though ivabradine reduced heart rate in a dose-dependent manner when it was given in the range of 'therapeutic' doses. Although ivabradine can reduce heart rate in patients in whom β-blockers are ineffective (this is one of its preferential clinical indications), this reduction is usually an additive effect when concomitantly administered with a β-blocker, at least when a residual sympathetic tone is still significant in these patients. Indeed, it is important to consider that the use-dependency resulting from the specific features of HCN4 inhibition with ivabradine is a useful property regarding its clinical efficacy and safety, and it predicts a greater rate-reducing ability at higher heart rate and conversely a more limited effect at a lower heart rate, as was clearly confirmed in patients. Finally, as expected from a drug that acts selectively on pacemaker I_f current, ivabradine does not induce significant prolongations of the corrected QT interval and does not modify the PR interval at doses that clearly reduce heart rate, demonstrating its lack of negative dromotropic properties.[3]

2. Preservation of Contractility, Left Ventricular Relaxation, Stroke Volume and Cardiac Output

Because I_f channels present in the left ventricle (LV) are not activated under physiological conditions, ivabradine is devoid of significant effect on myocardial contractility and LV isovolumic relaxation as observed both *in vitro* (isolated rat left atria, guinea-pig papillary muscles)[1] and *in vivo*,[7,9,10] both at rest and during exercise.[10] Hence, one of the most important haemodynamic consequences of its ability to reduce heart rate selectively, is that ivabradine increases stroke volume and preserves cardiac output, both at rest and during exercise (figure 1), after both short- and long-term administration, and in both normal and failing hearts.[7,11] This pharmacological property of ivabradine is certainly one of the main differences between the haemodynamic profile of ivabradine and a β-block-

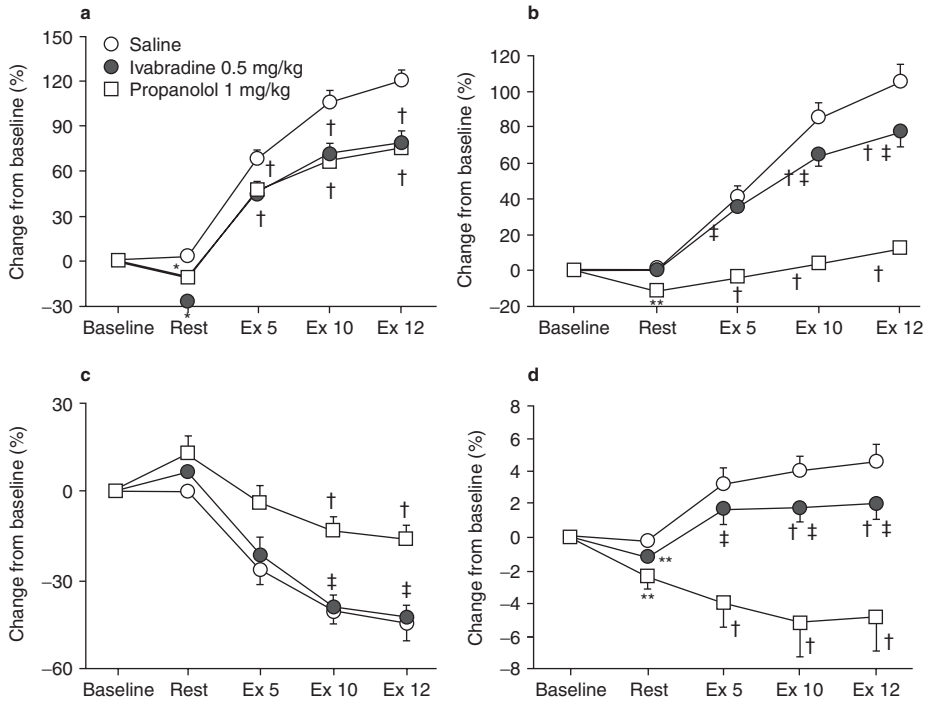

Fig. 1. Percentage changes from baseline of (**a**) heart rate, (**b**) left ventricular peak dP/dt, (**c**) mean coronary resistance and (**d**) coronary artery diameter at rest and during treadmill exercise at 5, 10 and 12 km/h (Ex 5, 10 and 12, respectively) after intravenous administration of saline, ivabradine 0.5 mg/kg or propranolol 1 mg/kg in conscious dogs. * $p < 0.05$ vs baseline; † $p < 0.01$ vs saline; ‡ $p < 0.01$ vs propranolol (reproduced from Simon et al.,[7] with permission).

er, because the latter simultaneously reduces heart rate and contractility and thus reduces both cardiac output and stroke volume when the sympathetic tone increases.[7] A similar haemodynamic profile with a dose-dependent increase in stroke volume and preservation of cardiac output was reported by Mulder et al.[11,12] after short- and long-term (3 months) treatment with ivabradine in a rat model of chronic heart failure.

Regardless of the clinical context, i.e. normal or failing hearts in animals and patients, ivabradine decreases heart rate and preserves cardiac output without any change in measured arterial blood pressure and calculated peripheral vascular resistance. This illustrates the lack of vascular tropism of this drug because I_f channels are absent, or not functional, at the vascular level. This excludes any role of LV workload in the observed increase in stroke volume by ivabradine, and explains why this improvement in LV function is also observed in isolated heart preparations at fixed preload and afterload.[12]

3. Effects of Ivabradine on the Balance of Myocardial Oxygen Supply/Demand

At the cardiac level, heart rate is a key determinant of the oxygen demand component and plays a dual role in the balance between myocardial oxygen supply and demand. On one hand, any change in heart rate directly influences coronary blood flow, as this flow depends on the diastolic perfusion time of the vascular coronary bed. On the other hand, any change in heart rate indirectly modifies coronary blood flow through metabolic autoregulation, because myocardial oxygen consumption is closely associated with cardiac rate.

For a long time, administration of β-blockers was the only available pharmacological tool to decrease heart rate. However, the simultaneous blockade of both β_1- and β_2-adrenoceptors at the cardiac and coronary artery level did not afford the possibility of differentiating between the respective contributions to myocardial oxygen demand of reductions in cardiac rate and contractility. Using ivabradine, it was recently possible to investigate the contribution of these two major determinants of myocardial oxygen demand. Because ivabradine has no direct effect on myocardial contractility or coronary vessels in physiological conditions,[1,7] it was now possible to investigate this fundamental question by comparing the effects of atenolol and ivabradine on myocardial oxygen consumption ($M\dot{V}O_2$). For this purpose, Colin et al.[13] compared the effects of atenolol and ivabradine on $M\dot{V}O_2$ when administered at doses that reduced heart rate to the same levels at rest and during treadmill exercise, in a model of conscious instrumented dogs for the simultaneous recording of coronary blood flow (Doppler) and sampling of blood from the aorta and the coronary sinus, and for calculating the arteriovenous difference in oxygen content. For a similar reduction in heart rate (approximately −30%) and mean LV ejection wall stress (i.e. LV afterload) during exercise, they observed an equal and additive contribution of the reduction in myocardial chronotropy (ivabradine and atenolol) and inotropy (atenolol only) to limiting the exercise-induced increase in $M\dot{V}O_2$. These results mean that reductions in heart rate and myocardial inotropy almost equally participate to the decrease in myocardial oxygen demand during exercise in conscious dogs.

As shown in figure 2, a linear relationship was observed in this model between the reduction in heart rate provided by ivabradine within a wide range of doses and the corresponding decrease in $M\dot{V}O_2$.[14] This suggests that compared with β-blockers, an optimal dose of ivabradine cannot be defined, but rather a wide range of doses can be used, depending on the level of heart rate and/or $M\dot{V}O_2$ that needs to be achieved. This is a highly relevant clinical property of ivabradine, because its unique profile allows a precise dose adjustment to reduce $M\dot{V}O_2$ on the basis of observed reduction in heart rate, a parameter that can be easily predicted and measured in patients.

4. Effects of Ivabradine on Coronary Blood Flow

Unlike β-blockers, which decrease the diameter of large coronary arteries and blood flow through the combined blockade of vascular β_1- and β_2-adrenoceptors and unopposed α-adrenergic vasomotor tone,[15-17] I_f inhibition with ivabradine does not directly interfere with coronary vasomotion because this current is not present on vascular smooth muscle cells.[1,7] Nevertheless, because the reduction in heart rate and thus the prolongation of diastolic perfusion time (DPT) of the coronary vascular bed (figure 3), ivabradine, like β-blockers, promotes a redistribution of transmural coronary blood flow (i.e. it increases the endocardial/epicardial blood flow ratio) by limiting the reduction in subendocardial flow during myocardial ischaemia.[18] Despite this common property, there is a major difference between these drugs in their effect on DPT because ivabradine can reduce heart rate without significant changes in myocardial inotropy and lusitropy, whereas β-blockers cannot. Indeed, when ivadabrine and atenolol were administered at doses

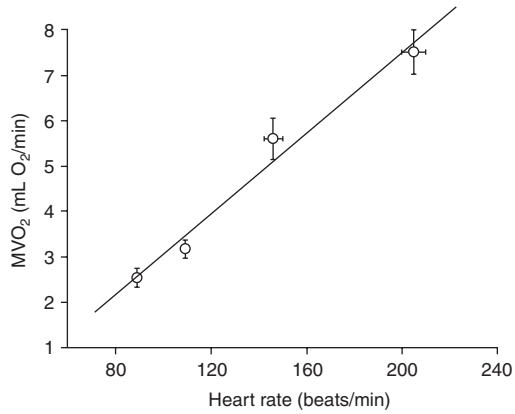

Fig. 2. Linear relationship between myocardial oxygen consumption ($M\dot{V}O_2$) and heart rate measured at rest and during exercise after administration of increasing doses of saline or ivabradine (0.25–1 mg/kg) in conscious dogs (reproduced from Colin et al.,[14] with permission).

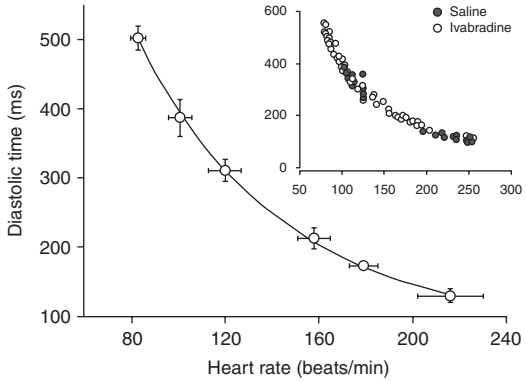

Fig. 3. Curvilinear relationship between diastolic perfusion time and heart rate at rest and during exercise after administration of increasing doses of saline or ivabradine (0.25–1 mg/kg) in conscious dogs (reproduced from Colin et al.,[14] with permission).

that induced exactly the same reduction in heart rate during a treadmill exercise in conscious dogs, Colin et al.[13] observed that ivabradine increased DPT by 10% (i.e. 6 sec/min) more than atenolol (figure 4). These differences are a direct consequence of the negative inotropic and lusitropic properties of atenolol, because the increase in DPT induced by ivabradine was totally blunted by atrial pacing, whereas a significant reduction in DPT persisted when the reduction in heart rate induced by atenolol was abolished by atrial pacing.[13] However, it is important to remember that the different effects of ivabradine and atenolol on DPT (as well as on $M\dot{V}O_2$) are only relevant and significant during exercise, i.e. when ventricular loading conditions and sympathetic tone are at their maximal levels.

Such a difference in effect on DPT between drugs (10%) can be considered as negligible under physiological conditions. However, in experimental studies conducted in conscious dogs, it was demonstrated that approximately 1% of the increase in DPT by reduction of heart rate corresponded to a 6% increase in subendocardial blood flow,[19] a value which might be critical at the ischaemic threshold. Conversely, a reduction of DPT by 2–5% at the ischaemic threshold might induce a dramatic drop in the coronary vasodilator reserve and induce myocardial ischaemia, especially within the subendocardium in patients with severe coronary disease.[20]

5. Effects on Myocardial Ischaemia and Stunning

Although I_f inhibitors and β-blockers reduce $M\dot{V}O_2$ and improve myocardial oxygen supply through quite different mechanisms, they both contribute to the reduction in the severity of ischaemic injury (reduction of ST segment elevation, preservation of tissue adenosine triphosphate [ATP] levels, reduction of regional contractile dysfunction) regardless of the experimental[9,18,21,22] or the clinical[8,23] trial design used. However, there is a major difference between these two antianginal drugs with regard to myocardial stunning, the reversible but long-lasting regional contractile dysfunction that occurs despite a complete reperfusion of the previously ischaemic myocardium and the absence of tissue necrosis. Indeed, in an experimental model of myocardial ischaemia induced by the combination of a coronary stenosis and 10 minutes of exercise on a treadmill (slope 13%) in conscious dogs, Monnet et al.[18,21] reported that both atenolol and ivabradine,

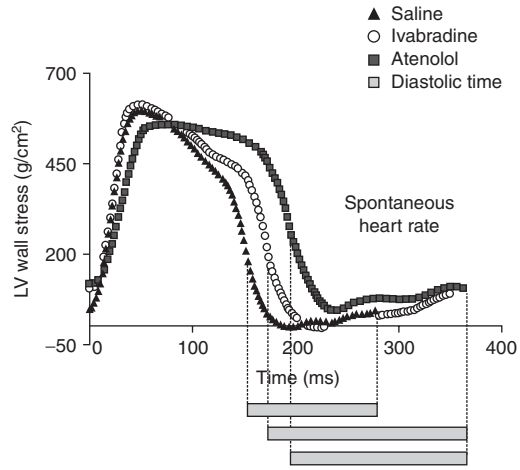

Fig. 4. Left ventricular wall stress versus time during a single representative beat during treadmill exercise in conscious dogs at spontaneous heart rate. Recordings were superimposed and performed every 2 msec after administration of saline and ivabradine or atenolol in doses with equivalent negative chronotropic effects. Both drugs increased the diastolic perfusion time compared with saline, but for a similar heart rate reduction the diastolic perfusion time was 10% longer (6 sec/min) with ivabradine than atenolol, and this difference persisted during atrial pacing (reproduced from Colin et al.,[13] with permission).

administered at doses that reduced heart rate to the same extent (–30%), redistributed myocardial blood flow towards the subendocardium and reduced myocardial dysfunction (assessed by sonomicrometry) during the ischaemic period. However, atenolol worsened myocardial stunning during the recovery period in these animals, whereas ivabradine decreased the severity and duration of stunning in the same conditions (figure 5a). This important difference between these drugs was mainly related to the β_1-adrenergic blockade-mediated negative inotropic and lusitropic effects of atenolol, which was considerably amplified when the negative chronotropic effect of atenolol was abolished by atrial pacing (figure 5b). In contrast, ivabradine reduces myocardial stunning through its ability to reduce heart rate selectively (this effect was also abolished by atrial pacing) as well as its inability to alter myocardial inotropy and lusitropy. Moreover, these differential effects of atenolol and ivabradine on myocardial stunning were independent of their ability to reduce myocardial ischaemia, because this difference persisted, and was even magnified, when the drugs were administered at the end of the exercise and when the coronary stenosis was released (figure 5).

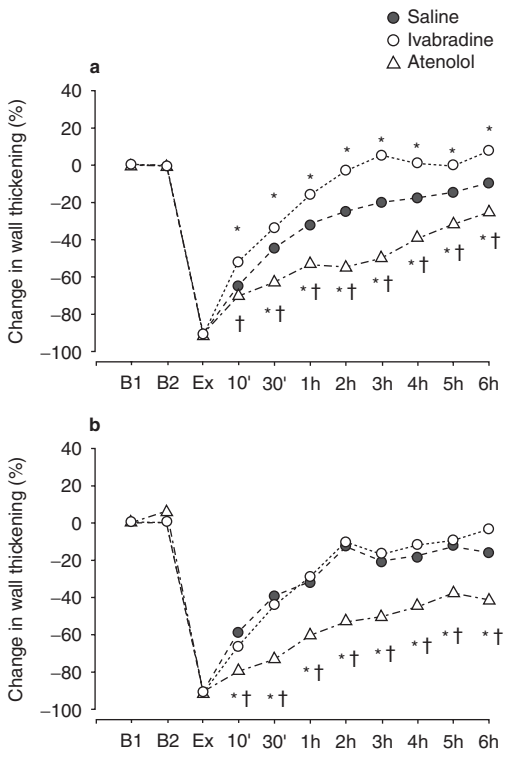

Fig. 5. Evolution of wall thickening (% change from baseline) in the ischaemic zone measured before (B1) and after (B2) administration of saline, ivabradine and atenolol in conscious dogs during exercise at spontaneous heart rate (**a**) and under atrial pacing (**b**). * $p < 0.05$ vs saline; † $p < 0.01$ atenolol vs ivabradine (reproduced from Monnet et al.,[21] with permission).

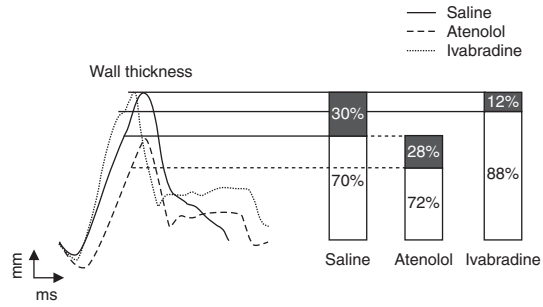

Fig. 6. Comparative distributions of systolic and post-systolic wall thickening. Bar graphs are derived from representative waveforms recorded from the same dog during three sequences: saline, atenolol and ivabradine administration (reproduced from Lucats et al.,[25] with permission).

More recently, Lucats et al.[24,25] reported that besides the reduction of systolic performance of the stunned myocardium, ivabradine was also able to reduce post-systolic wall thickening (PSWT), a major diastolic wall motion that is considerably amplified during myocardial ischaemia and stunning. PSWT is a paradoxical contraction occurring during diastole after aortic valve closure, thus representing a waste of thickening that impedes early relaxation and ultimately leads to abnormal ventricular filling. Indeed, ivabradine converted PSWT into an efficient ejectional thickening when administered during myocardial stunning induced in conscious dogs (i.e. a lower part of thickening was wasted after aortic valve closure). However, atenolol was unable to reduce PSWT in the same conditions, because of its negative inotropic properties (figure 6). In other words, ivabradine did not increase the residual systolic wall thickening of the stunned myocardium by requiring an additive inotropic effort but it used the already existing wall thickening by transferring a part of the diastolic thickening into the ejection

period. This reorganisation of the regional contractile function during stunning was totally dependent on the ivabradine-induced reduction in heart rate, as it was abolished by atrial pacing. In contrast, atenolol did not protect the stunned myocardium against the waste of thickening, as the ratio of PSWT to total wall thickening remained unchanged when compared with saline, used as a placebo, despite an increase in diastolic time similar to that with ivabradine in the same experimental model.[25]

6. Effects on Myocardial Infarction, Mortality and Left Ventricular Remodelling

As mentioned in section 2, Mulder et al.[11,12] have confirmed that one of the major haemodynamic properties of ivabradine is related to its ability to increase stroke volume and preserve cardiac output after both short- and long-term treatment in rats with chronic heart failure (permanent coronary artery occlusion). These investigators have clearly demonstrated that several mechanisms may account for these effects of ivabradine. After short-term treatment (4 days), the increase in stroke volume was associated with an increase in LV diastolic diameter without change in LV systolic diameter, suggesting a Frank-Starling mechanism. In contrast, after long-term treatment (90 days), the preservation of stroke volume and cardiac output, despite sustained reduction in heart rate, was associated with a decrease in LV systolic diameter without change in LV diastolic diameter. Such a profile of response suggests a progressive change of the LV structure associated with a remodelling process as usually observed in chronic heart failure, because ivabradine decreased LV collagen density and increased LV capillary density without modifying LV weight. Indeed, while interruption of long-term treatment with ivabradine resulted in a rapid return of heart rate to basal levels, cardiac output still remained significantly increased as a result of the preservation of stroke volume at the level observed in animals receiving long-term treatment with ivabradine.[11] Hence, this improvement in cardiac function was related not only to the reduction in heart rate *per se* but also to favourable effects on LV remodelling and improvement of coronary perfusion (preservation of coronary endothelial dysfunction and prevention of local hypoxia) as a consequence of long-term heart rate reduction. Furthermore, in terms of improved oxygen supply/demand ratio and tissue protective effects, the improvement in LV filling induced by the decrease in heart rate diminished the level of sympathetic activity, as suggested by a simultaneous decrease by 15% in plasma noradrenaline (norepinephrine) levels.[11]

Indeed, one of the important indirect effects of long-term reduction in heart rate with ivabradine on myocardial structure is its effect on prevention of loss of coronary vessels within the remaining 'viable' part of the failing myocardium, a property that is probably closely linked to the observed angiogenesis in healthy animals receiving long-term treatment with a drug that decreases heart rate.[26-28] As suggested by Mulder et al.,[12] one potential and original mechanism involved in this prevention of coronary rarefaction could be the augmented levels of hypoxia-inducible factor-1α and associated growth factors through the increase in LV diastolic diameter and thus in myocardial stretch, which is a well known trigger for multiple factors involved in angiogenesis. Associated with a reduction in oxygen requirements and improvement in the oxygen supply-demand balance, this effect of long-term heart rate reduction with ivabradine can improve or at least preserve the 'coronary reserve' associated with a decrease in perivascular collagen in the surviving myocardium, thus preventing the progressive degradation of the cardiac function in heart failure.[12]

The protective effect of ivabradine after myocardial infarction has also been demonstrated after long-term coronary occlusion (28 days) in rabbits.[28] In this experimental model, the investigators demonstrated that ivabradine as well as metoprolol not only preserved LV function and dilatation (reduction of the brain natriuretic factor production) but also significantly reduced mortality and infarct size. Interestingly, the expression of the V_3/V_1 ratio of myosin heavy chain isoenzymes was less important in ivabradine- and metoprolol-treated rabbit

myocardium than in corresponding controls, suggesting that 'economic' contraction was better preserved after sustained reduction in heart rate.

7. Prevention of Endothelial Dysfunction Induced by Dyslipidaemia

Recently, Thorin et al.[29] reported that 3 months of treatment with ivabradine totally prevented cerebrovascular endothelial dysfunction associated with atherosclerosis and led to concomitant restoration of the endothelium-dependent dilatory hydrogen peroxide pathway in dyslipidaemic mice expressing the human apo B-100 protein. In the same model, they also demonstrated that ivabradine prevented endothelial dysfunction in renal arteries by reducing the oxidative stress.[30] These surprising and unexpected data – observed following administration of a drug that exhibits no direct pharmacological effects on regional vascular beds – indicate that long-term pharmacological reduction in heart rate interacts with *a priori* unexpected mechanisms involved in vascular remodelling associated with chronic disease. Whether these properties are shared with β-blockers cannot be answered at present.

8. Conclusion

The anti-ischaemic properties of ivabradine are now well established, both in animals and in humans.[31] The time is ripe to investigate a new era of pharmacology in which totally unexpected properties of this original drug will reveal the benefit of long-term selective reduction in heart rate on organs or systems *a priori* excluded from its initial classical field of action. Because ivabradine is also very well tolerated in patients, these new pharmacological properties will probably benefit numerous patients with chronic diseases in, and possibly beyond, the cardiovascular fields. These preclinical studies demonstrate that ivabradine has certain advantages over existing antianginal therapies that could be of interest in clinical practice.

Acknowledgements

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