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COMMENTARY

Pleiotropic action(s) of the bradycardic agent ivabradine: cardiovascular protection beyond heart rate reduction

G Heusch

Institute for Pathophysiology, University of Essen Medical School, Essen, Germany

The bradycardic agent ivabradine has proved to be of benefit in experimental models with the end points of ischaemic myocardial blood flow and contractile function, infarct size, post-infarct remodelling and atherosclerosis. The benefits to ischaemic myocardial blood flow and contractile function are strictly heart rate dependent; those on infarct size are partly heart rate independent. The heart rate dependency of ivabradine's benefit for atherosclerotic vascular function is contradictory, and that on post-infarct remodelling is entirely unclear.
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Both the detrimental effects of increased heart rate and the beneficial effects of heart rate reduction in the setting of coronary artery disease are well established (Heusch, 2008). The classical treatment to achieve heart rate reduction is by blockade of β-adrenoceptors (β-blockade), and β-blockade along with a reduced heart rate improves blood flow and contractile function of ischaemic myocardium and reduces infarct size (Schulz *et al.*, 1995). However, β-blockade has negative inotropic effects that are unwanted when ischaemia *per se* impairs ventricular function. Also, when heart rate reduction is eliminated by atrial pacing, β-blockade exerts negative effects on regional myocardial blood flow and function, largely through unmasked α-adrenergic coronary vasoconstriction (Heusch *et al.*, 2000). Another option—apart from β-blockade—for the reduction of heart rate and attenuation of myocardial ischaemia is the use of calcium antagonists. Calcium antagonists functionally antagonize coronary vasoconstriction mediated through α-adrenoceptors and are thus devoid of this undesired effect, but the compounds are nevertheless negative inotropes. These undesired effects of β-blockers and calcium antagonists have prompted the development of drugs that reduce heart rate more selectively (Heusch, 2008). Several more selective bradycardic agents that reduce heart rate through inhibition of the pacemaker current I_f in the sinus node have demonstrated beneficial outcomes in experimental models of myocardial ischaemia/reperfusion in terms of improved blood flow and contractile function (Guth *et al.*, 1987) and reduced infarct size (Schulz *et al.*, 1995; Heusch *et al.*, 2008). Also, beneficial effects of selective bradycardic agents in more long-term models of post-myocardial infarction remodelling have been reported.

The only selective bradycardic agent that is currently available for clinical use is ivabradine and this drug attenuates exercise-induced myocardial ischaemia in patients with chronic stable angina and is not inferior to atenolol and amlopidine in the treatment of chronic stable angina (Heusch, 2008).

Is there evidence for heart rate-independent myocardial effects of ivabradine?

The selectivity of a selective bradycardic agent refers, of course, to reducing heart rate and as such to a selective reduction of the I_f current in the sinus node. However, under certain circumstances, such as ischaemia or heart failure, the normally low expression of hyperpolarization-activated cyclic nucleotide-gated channels (which carry the I_f current) outside the sinus node is increased (Cerbai *et al.*, 2001). Such left ventricular I_f-carrying channels can also contribute to calcium currents (Michels *et al.*, 2008) and possibly to calcium overload. Potentially, then, part of the observed beneficial effects of ivabradine could be independent of heart rate reduction and be exerted directly on left ventricular myocardium. The strictest and most robust proof for heart rate selectivity of ivabradine's effects with respect to each end point is the complete reversal of ivabradine's effects by atrial pacing back to the original heart rate. In fact, such

Correspondence: Professor Dr G Heusch, Institut für Pathophysiologie, Universitätsklinikum Essen, Hufelandstrasse 55, 45122 Essen, Germany.
E-mail: gerd.heusch@uk-essen.de
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rigorous proof for the heart rate selectivity of ivabradine's effects has been established for ischaemic blood flow and ischaemic or post-ischaemic contractile function (Heusch *et al*., 2008).

In an established pig model of regional myocardial ischaemia/reperfusion, ivabradine improved regional blood flow and contractile function proportionately, and this beneficial effect was entirely reversed by atrial pacing. Also, ivabradine when given either before or after the onset of ischaemia reduced infarct size, but this beneficial effect was only partially reversed by atrial pacing. Ivabradine when given just before reperfusion also reduced infarct size and this beneficial effect persisted and was not reversed by atrial pacing. Apparently, the reduction in infarct size by ivabradine is only partially mediated by heart rate reduction during myocardial ischaemia, but to a significant extent also by an yet undefined beneficial action on reperfusion injury (Heusch *et al*., 2008), reminiscent of the protection provided by post-conditioning (Skyschally *et al*., 2008). Unfortunately, no data have been reported so far on the potential persistence of ivabradine's beneficial effects on post-myocardial infarction remodelling when heart rate is not reduced.

Is there evidence for heart rate-independent vascular effects of ivabradine?

Also, in the context of atherosclerosis and vascular disease in more general, the functional role of I_f-carrying channels and potential targets of ivabradine remain to be elucidated. Two recent studies have reported effects of ivabradine on vascular function. In dyslipidaemic mice, the impairment of ACh-induced, endothelium-dependent vasodilation of cerebral and renal arteries was restored by ivabradine, but not by metoprolol at equal heart rate reduction, suggesting that ivabradine's action was not related to heart rate reduction (Drouin *et al*., 2008). Again in dyslipidaemic mice, cholinergic endothelium-dependent vasodilation was restored by ivabradine; vascular NADPH oxidase activity and free radical production as well as atherosclerotic lesion formation were reduced. In this particular study, a direct effect of ivabradine on vascular function and free radical formation was not observed and thus ivabradine's action was related to attenuation of vascular shear stress along with heart rate reduction (Custodis *et al*., 2008).

In conclusion, there is good evidence for heart rate-independent pleiotropic effects of ivabradine on infarct size, whereas pleiotropic effects on other important end points (remodelling, vascular function) remain to be further analysed.

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