

# Ivabradine (Procoralan) alone or with $\beta$ -blockers in myocardial ischemia

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## Abstract

Both ivabradine (Procoralan), the first I(f) current inhibitor of the cardiac pacemaker cells, and  $\beta$ -blockers reduce heart rate and exhibit potent anti-ischemic effects. Although  $\beta$ -blockers are still the first choice of medication to treat patients suffering from myocardial ischemia, numerous experimental and clinical arguments are now available from which to conclude that ivabradine not only is the drug of choice when  $\beta$ -blockers are not well tolerated or contraindicated, but is the drug that can be associated with  $\beta$ -blockers at the commonly used dosage in clinical practice for an optimal therapeutic efficacy in ischemic disease.

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**Keywords:** Angina pectoris,  $\beta$ -blockers, ivabradine (Procoralan), myocardial ischemia

## Introduction

Because an increase in diastolic perfusion time simultaneously reduces myocardial oxygen demand and increases oxygen supply, a reduction in heart rate has always been a primary pharmacological target for the treatment of myocardial ischemic disease (Figure 1). All available epidemiological studies demonstrate that, after myocardial infarction or in heart failure, heart rate reducing therapies such as  $\beta$ -blockers reduce cardiac mortality [1].  $\beta$ -Blockers remain the drugs of first choice to treat patients suffering with myocardial ischemia and have been for at least 40 years, although their usefulness is often limited by their numerous side effects or contraindications. These limitations are usually linked to the fact that the pharmacological blockade of  $\beta_1$ -adrenoreceptors,

which is the basis of heart rate reduction, is always associated with reductions in myocardial contraction/relaxation and conduction time, limiting their therapeutic usefulness in ischemic patients with altered basal contractile function, rhythmic disorders, or both, even though  $\beta$ -blockers are also indicated in heart failure and some rhythmic disorders. More recently, a reduction in the rate of admission to hospital of patients with coronary artery disease with a cardiac rate greater than 70 beats/min was reported in a subgroup analysis of the Morbidity-Mortality Evaluation of the I(f) Inhibitor Ivabradine in Patients with CAD and Left Ventricular Dysfunction (BEAUTIFUL) study after treatment with the I(f) current inhibitor, ivabradine (Procoralan), a pure heart rate reducing drug [2].

The discovery of ivabradine, which can selectively reduce heart rate without concomitant negative

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### Ivabradine in ischemic heart disease

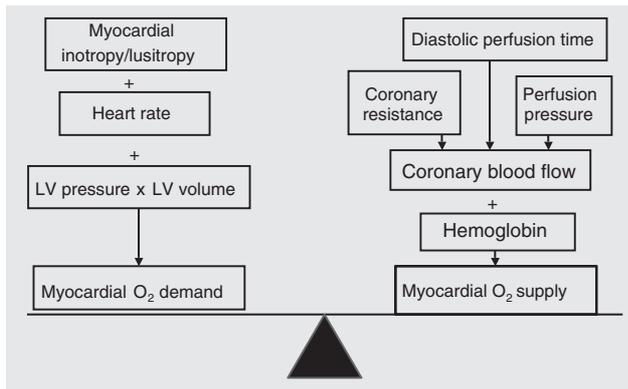


Figure 1. Main determinants of the balance between myocardial oxygen supply and demand. LV, left ventricular.

effects on myocardial contraction/relaxation, conduction time, and coronary vasomotor tone [3–5], was thus a truly innovative discovery among drugs previously used for the treatment of myocardial ischemia. This also partly explains why, after the introduction of ivabradine as a new antianginal drug, the initial medical opinion was to consider ivabradine and  $\beta$ -blockers as mutually exclusive. However, because of a real synergy in their mechanisms of action, this concept was totally revisited recently, leading now to their use as combined therapy, especially in patients with angina pectoris who cannot tolerate a full dose of  $\beta$ -blockers.

### Ivabradine versus $\beta$ -blockers

Although both ivabradine and  $\beta$ -blockers improve the balance between oxygen supply and demand during myocardial ischemia, they promote this result through quite different mechanisms. As shown in Table 1,  $\beta$ -blockers, regardless of their pharmacological spectrum, reduce myocardial oxygen consumption ( $mVO_2$ ) by simultaneously reducing cardiac rate and contractility. They also increase coronary vascular resistance, through the direct blockade of  $\beta$ -adrenoreceptors and indirect unmasking of  $\alpha$ -adrenoreceptors [6,7].

As a result,  $\beta$ -blockers usually reduce coronary blood flow or at least limit its increase during exercise, but their simultaneous and potent reduction of  $mVO_2$  always leads, through metabolic autoregulation, to an improvement in the global transmural perfusion per unit of cardiac work, especially within the endocardial layers.

At least three main mechanisms illustrate the contrast between  $\beta$ -blockers and ivabradine (Table 1):

- Ivabradine reduces  $mVO_2$  through its selective reduction of the heart rate.
- Ivabradine preserves the maximal reserve of coronary vasodilatation at exercise because there are no I(f) channels on these arteries and thus no coronary constriction – a difference from  $\beta$ -blockers.
- Ivabradine causes a greater increase (exactly 10%) in the diastolic perfusion time of the coronary vascular bed for the same reduction in heart rate compared with  $\beta$ -blockers, because the diastolic filling time of coronary arteries in protodiastole is significantly longer (6 s/min) with ivabradine than with a  $\beta$ -blocker such as atenolol [8]. These differences are of major importance when the relationship between coronary blood flow (or myocardial oxygen supply) and  $mVO_2$  reaches the ischemic threshold for a patient with limited exercise-induced angina pectoris [9].

Taking these differences together, for a similar reduction in heart rate ivabradine probably improves the balance between oxygen supply and demand to the ischemic myocardium more favorably than do  $\beta$ -blockers. This could partly explain why ivabradine tended to exert more anti-ischemic effects than atenolol in the 939 patients with angina pectoris who were included in the International Trial on the Treatment of Angina with Ivabradine vs. Atenolol (INITIATIVE), although this large trial finally concluded that the difference in efficacy between the drugs was non significant, regardless of the exercise test and the challenges of doses used [10].

Table 1. Comparative anti-ischemic effects of ivabradine and  $\beta$ -blockers at equivalent reduction of heart rate

|   | $\beta$ -blockers | Ivabradine |
|---|-------------------|------------|
| Heart rate  | ↓                 | ↓          |
| Myocardial contractile force  | ↓                 | 0          |
| Relaxation  | ↓                 | 0          |
| Myocardial oxygen consumption   | ↓↓                | ↓          |
| Coronary vascular resistance  | ↑                 | 0          |
| Ejection/diastolic perfusion time ratio   | ↑                 | ↓↓         |
| Myocardial distribution of flow between endo- and epicardium                      | ↑                 | ↑          |
| Anti-ischemic effect (reduction in ST-segment) for a similar heart rate reduction | ↓↓                | ↓↓↓        |
| Increase in myocardial oxygen supply for a similar heart rate reduction           | ↑                 | ↑↑         |

## Ivabradine in combination with $\beta$ -blockers

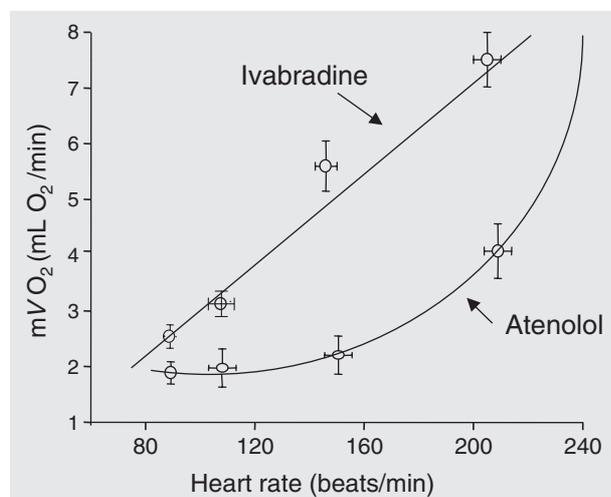
Inasmuch as a half-filled bottle can be viewed as half full or half empty, the pharmacological spectra of ivabradine and  $\beta$ -blockers as viewed above can also be viewed as complementary or even additive. Indeed, both drugs reduce myocardial ischemia and infarct size [11] and reduce heart rate.

With this in mind, and because any decrease in myocardial oxygen demand per unit of heart rate reduction is the most important endpoint to reach for reducing exercise-induced myocardial ischemia, we compared the relationships between reductions in measured  $mVO_2$  and heart rates in normal conscious dogs during repeated treadmill exercises at different workloads when ivabradine and atenolol were administered separately and at doses inducing the same final reduction in heart rate [12,13]. As shown in *Figure 2*, this relationship is negatively and linearly related with ivabradine, but hyperbolic with atenolol and thus, for a small reduction in heart rate, there is a strong reduction in  $mVO_2$  with the latter, above all when basal heart rate is high. Unfortunately, we did not investigate this relationship when the drugs were administered together at a chosen dose inducing the same heart rate reduction as when they were administered separately, but one can postulate that, at lower doses for each drug, their combination should induce a larger reduction in  $mVO_2$  than when they are administered separately. Such a scenario could possibly explain the recent data reported in ASSOCIATE study in which 889 patients with stable angina receiving atenolol 50 mg/day were allocated randomly to groups to receive either a placebo or ivabradine 5 mg twice daily for 2 months, which was then increased to 7.5 mg twice daily for a

further 2 months. On the basis of the results with classical treadmill exercise tests, it was concluded that the combination of 7.5 mg twice daily ivabradine and atenolol administered at the commonly used dosage in clinical practice in patients with chronic stable angina pectoris produced additional efficacy, with no untoward effect on safety or tolerability [14].

## Conclusion

From experimental studies, we have learned that ivabradine and  $\beta$ -blockers possess complementary and perhaps even additive pharmacological properties linked to their common ability to reduce heart rate: in the short term, they improve the balance between oxygen supply and demand in the ischemic myocardium [5,11–13]; in the long term, they reduce the activity of the renin–angiotensin system [15–17], they reduce oxidant stress and endothelial dysfunction [18], and they reduce left ventricular remodeling of the post-infarcted myocardium [15–17]. From the BEAUTIFUL study, we learned that ivabradine in combination with  $\beta$ -blockers is safe for the patient and may afford a further reduction in their risk of admission to hospital [2]. From the ASSOCIATE study, we learned that ivabradine associated with atenolol produces additional efficacy in patients with chronic stable angina pectoris [14]. Thus it is time now to consider that ivabradine not only is the drug of choice when  $\beta$ -blockers are not well tolerated by or are contraindicated in a patient, but is the drug that can be combined with  $\beta$ -blockers for an optimal therapeutic effect in patients with ischemic disease. ■



*Figure 2.* Relationship between heart rate and myocardial oxygen consumption ( $mVO_2$ ) after the administration of ivabradine or atenolol in conscious dogs at rest and during exercise.

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