The role of ivabradine in improving myocardial perfusion, adding to the antianginal benefits

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The most common cause of oxygen demand/supply mismatch is atherosclerotic narrowing of the coronary artery, resulting in decreased coronary blood flow. However, endothelial dysfunction and/or microvascular dysfunction may be responsible for myocardial ischaemia and importantly may often coexist in patients with angina. Coronary flow reserve reflects the functional capacity of coronary circulation to adapt to the blood demand during increased cardiac work. In addition, coronary flow reserve predicts long-term adverse cardiovascular outcome. Therefore, a clear understanding of myocardial perfusion pathophysiology and a knowledge of the antianginal–anti-ischaemic drugs effect on coronary circulation are crucial for the judicious use of medications for the treatment of angina patients with coronary artery disease. This article discusses the role of ivabradine in improvement of myocardial perfusion based on data drawn from relevant preclinical and clinical investigations. Experimental data suggest that heart rate reduction with ivabradine causes greater increase in duration of diastolic perfusion time and coronary flow compared with β-blockade due to absence of impairing of left ventricular contractility and coronary vasomotion. In consequence, the full benefits of heart rate reduction for improved coronary perfusion could be realized with ivabradine. Following experimental data, clinical studies demonstrated anti-ischaemic and antianginal efficacy of ivabradine in patients with stable coronary artery disease. These clinical benefits have been supported by recent clinical data on improvement of coronary flow reserve, and coronary collateral circulation with ivabradine supports the role of ivabradine as an important anti-ischaemic and antianginal agent in patients with angina in addition to other recommended therapies or revascularization.

Introduction

The myocardium depends on the coronary blood flow for its function and 5–10% of the cardiac output is directed to the coronary vessels. These vessels during the epicardial course giving rise to smaller vessels (microcirculation) in order to supply the capillary network (with a diameter of only 5 μm) of the heart with blood.1

Coronary blood flow is not constant over time but is adapted to the metabolic needs of the myocardium. The control system of the heart has the ability to regulate coronary blood flow to a level close to the minimum required for the supply of oxygen.

The microcirculation (vessels <200 μm in diameter) consists of a channel of passive networks and is an active site of blood flow control, through a number of metabolic, myogenic, and other mechanisms. This is achieved by a strong and immediate response of the smooth muscles located in the arterioles wall (autoregulation).2,3

Cardiac contraction by itself imposes an important physiological restraint on coronary blood flow. The generating factors of the left ventricular pressure compress the vessels within the heart muscle (extravascular resistance). Consequently, coronary blood flow is impeded during systole and the flow in the coronary vessel occurs predominantly in diastole.

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At rest, the ability of blood flow regulation is high, since 60% of total myocardial vascular resistance is offered by arterioles.

During exercise, myocardial oxygen consumption increases and has to be accompanied by an increase of coronary blood flow. However, when hyperaemia is induced, changes in microvascular resistance through smooth muscle vasodilation result in dilatation of the arterioles and venules. The total myocardial vascular resistance decreases and capillary resistances now comprise 75% of the total resistance. Thus, capillaries offer the most resistance to coronary blood flow during hyperaemia and constitute the barrier to hyperaemic blood flow. 1,2 Both functional and structural vascular changes may interfere with coronary blood flow regulation. 3,4

One of the major determinants of myocardial oxygen consumption and myocardial blood flow is heart rate. An increase in heart rate increases not only the metabolic demand for blood flow but also decreases myocardial perfusion time. Hence, by increasing heart rate, arteriolar dilatation must compensate for both of these effects.

It is clear that under normal conditions, coronary blood flow is much lower than maximum and the coronary vessels are able to adapt the flow to metabolic demands. The extent of which coronary blood flow can increase above resting flow requirements is by definition the coronary flow reserve.

The most common pathophysiological mechanism affecting the coronary blood flow supply is atherosclerosis. Atherosclerotic coronary artery disease may result in either local or more diffuse narrowing of the coronary arteries. The reduction of the coronary artery diameter by the atherosclerotic plaque adds to the resistance of the coronary system. The local flow control system will recognize such an obstruction as a reduction in pressure and respond by smooth muscle relaxation and vasodilatation (autoregulation). However, the additional resistance to flow places the barrier of hyperaemic blood flow to a lower level and coronary flow reserve is reduced. As the vessel lumen decreases, the compensatory mechanism will be exhausted and ischaemia may emerge even at rest.

In addition, significant neural as well endothelial and other humoral control mechanisms are implicated in coronary blood flow regulation and microvascular dysfunction may be responsible or contributes to myocardial ischaemia in different conditions. 5,6

Therefore, a clear understanding of myocardial perfusion pathophysiology and a knowledge of the antianginal–anti-ischaemic drugs effect on coronary circulation are crucial for the judicious use of medications for the treatment of patients with coronary artery disease.

Since heart rate is the main determinant of myocardial oxygen consumption, heart rate reduction is an established important therapeutic strategy in the prevention of ischaemia.

Ivabradine reduces heart rate by inhibition of the I_{if}-channels in the sinus node. The findings from experimental and clinical data with ivabradine are useful to elucidate mechanisms that may underlie the anti-ischaemic and antianginal effects. In addition, they indicate important pharmacological differences between ivabradine and β-blockade, explaining differences in clinical effects. The purpose of this article was to discuss the role of ivabradine in improvement of myocardial perfusion based on data drawn from relevant preclinical and clinical investigations.

### Diastolic perfusion time and coronary blood flow

Myocardial perfusion occurs predominantly in diastole. Diastolic perfusion time is a major determinant of blood flow; it has been estimated that a 1% increase in diastolic time fraction increases blood flow by 2.6–6% in the normal heart. Physiological changes in hazard ratio (HR) affect mainly the duration of diastole, leading to diastolic time prolongation at lower heart rate both in absolute terms and as a fraction of the cardiac cycle, facilitating myocardial perfusion.

The effects of ivabradine and atenolol on diastolic time have been compared in two experiments. 7,8 Ivabradine increased diastolic time both at rest and during treadmill exercise to a greater degree than atenolol, though heart rate was similar with both drugs. β-Blockers, due to their negative effect on myocardial contractility, tend to prolong systole, reducing their effect on diastolic time fraction relative to that of ivabradine for a similar HR reduction (Figure 1).

As a result, ivabradine causes a greater increase in coronary blood flow (Figure 2) and its efficacy in stable coronary artery disease has been recognized. 10,11

These differences are of major importance when the relationship between coronary blood flow and myocardial oxygen consumption reaches the ischaemic threshold for a patient with limited exercise induced myocardial ischaemia.

### Coronary vasomotion

In the coronary circulation, both a_{1} and a_{2} adrenoreceptors mediate vasoconstriction and a well-functioning endothelium counterbalances this constriction effect. When endothelial dysfunction emerges, this constriction effect of the adrenoreceptors is exaggerated especially during exercise. 6

![Figure 1](https://academic.oup.com/eurheartjsupp/article-abstract/17/suppl_G/G19/2949935/2949935)

Figure 1  Left ventricular wall stress vs. time during exercise. Both ivabradine and atenolol increased the diastolic time compared with saline, but for similar heart rate reduction, diastolic time was smaller with atenolol compared with ivabradine. Adapted with permission from Colin et al. 8
β-Blockers affect vasomotion in the coronary circulation. β-Blockade can unmask α-adrenergic vasoconstriction in epicardial coronary arteries and in the coronary microcirculation, an effect that is especially prominent in atherosclerotic vessels. In contrast, ivabradine does not unmask α-adrenergic vasoconstriction or impede β-1- or β-2-mediated vasodilation.

In experiments, β-blockade resulted in constriction of large and small coronary arteries during exercise, while ivabradine allowed vasodilation to occur during exercise despite similar effect on heart rate. The ability of ivabradine to preserve coronary dilatation during exercise is of major therapeutic importance in patients with coronary artery disease.

Coronary flow reserve

Coronary flow reserve reflects the functional capacity of coronary circulation to adapt to blood demand during increased cardiac work. In addition, coronary flow reserve predicts long-term adverse cardiovascular outcome.

In our clinical study, we examined the effects of ivabradine on coronary blood flow and flow reserve in patients with stable coronary artery disease. In this study, we assessed 21 patients with stable coronary artery disease of one or two vessels, amenable for percutaneous coronary intervention. Immediately following coronary angiography, the culprit vessel/s for coronary intervention was defined according to guidelines and a non-culprit vessel was selected for coronary flow measurements. The non-culprit vessel was selectively engaged with a guide catheter. Intracoronary nitroglycerine (200 μg) was given to prevent catheter-induced coronary artery spasm and to avoid changes in coronary artery diameter. A 0.014 in., 15 MHz Doppler guide wire was advanced through the catheter to the non-culprit vessel. Once resting flow velocity data had been collected, a 30 μg bolus injection of intracoronary adenosine was given to obtain data during hyperaemia. To confirm that maximal hyperaemia had been achieved, doses increasing in 30 μg increments were infused until a plateau in flow velocity was reached. All measurements were made in the non-culprit vessel: (i) during diagnostic coronary angiography (baseline); (ii) during programmed coronary intervention in the culprit vessel/s (before the procedure), 1 week after treatment with ivabradine (5 mg twice daily) at the same location at the intrinsic heart rate (ivabradine); and (iii) at a pacing heart rate similar to baseline (ivabradine-pace), accomplished by pacing the right atrial appendage via a temporary pacing lead. Time-averaged peak coronary flow velocity (APV, cm/s) was measured and coronary flow reserve (CFR) was determined as the ratio of APV at maximal hyperaemia (h-APV) to APV at rest (r-APV).

As expected, heart rate was significantly lower after treatment with ivabradine (78 ± 14 vs. 65 ± 9 b.p.m., P < 0.001). There was a significant effect of ivabradine treatment on both resting and maximal hyperaemia time-averaged peak coronary flow velocity. Resting-APV at ivabradine was significantly lower than at baseline. However, there was no significant difference in r-APV between ivabradine-pace and baseline. Hyperaemia-APV at ivabradine was significantly higher than at baseline. Similarly, h-APV at ivabradine was significantly higher than at baseline. Ivabradine treatment also had a significant effect on CFR. Coronary flow reserve after ivabradine was significantly higher than at baseline. Similarly, CFR at ivabradine-pace was significantly higher than at baseline.

Our data suggest that ivabradine treatment not only reduces resting coronary blood flow but also increases hyperaemic coronary flow, leading to coronary flow reserve.
improvement in patients with stable coronary artery disease. Also, although resting coronary blood flow returns to the pretreatment values after heart rate correction by pacing, the enhancement of hyperaemic coronary blood flow remains (Figure 5). Therefore, even after heart rate correction, CFR remains significantly higher than the pretreatment values, indicating improved microcirculation with ivabradine treatment. Although the underlying mechanism is hypothetical, the most probable explanation is the improvement of ventricular relaxation-diastolic function caused by ivabradine treatment. These data are consistent with experimental data on better effect of ivabradine on diastolic phase of cardiac cycle.\textsuperscript{17}

Similarly, in recently presented study by Tagliamonte et al.,\textsuperscript{18} coronary flow reserve was significantly better in ivabradine-treated compared with bisoprolol-treated patients with angina.

In contrast, \(\beta\)-blockers have shown conflicting data on coronary flow reserve. Coronary flow reserve is increased in patients with reduced ejection fraction but seems to be unaffected in patients with preserved left ventricular function.\textsuperscript{19,20}

**Coronary collateral function**

The development of collateral circulation represents a natural mechanism to compensate for the limitation of coronary flow with progression of coronary artery stenosis and is advantageous in protection myocardium from ischaemia.

The clinical and experimental data suggested that bradycardia enhances vascularity and myocardial perfusion and preserves myocardial function. Lamping et al.\textsuperscript{21} tested the hypothesis that bradycardia, by prolonging ventricular diastolic filling time and volume, promotes collateral vessel growth. He demonstrated that chronic bradycardia facilitates angiogenesis/arteriogenesis in collateral-dependent myocardium and preserves maximal perfusion. These experimental data are in line with a retrospective clinical study from Patel et al.\textsuperscript{22} They found that there is an association between bradycardia and growth of collateral vessels in patients with obstructive coronary artery disease.

The experimental data in ApoE2/2 mice demonstrated that ivabradine-induced heart rate reduction stimulates adaptive collateral artery growth.\textsuperscript{23}

Recently, the first study of the effect of ivabradine on the coronary collateral circulation in humans has been published. The results of this first-time clinical, placebo-controlled randomized study show that ivabradine improves coronary collateral flow index in patients with stable coronary artery disease and diminishes electrocardiographic signs of ischaemia\textsuperscript{24} (Figure 6).

These data also demonstrate the differential advantage of ivabradine confirmed by the lack of data on improvement of collateral circulation with \(\beta\)-blockers.\textsuperscript{25}

**Conclusion**

Experimental data suggest that pharmacological heart rate reduction with ivabradine resembles physiological rate changes more closely than with \(\beta\)-blockade, in that of physiological changes in diastolic time fraction, left

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**Figure 5** Resting (r) and maximal hyperaemia (h) time-averaged peak coronary flow velocity recordings at baseline (baseline) and after 1 week’s ivabradine treatment, both at the intrinsic heart rate (ivabradine) and at a paced rate similar to that of baseline (ivabr-pace). CFR, coronary flow reserve.
Conflict of interest: None declared.

References


