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Review

Ivabradine in chronic stable angina: Effects by and beyond heart rate reduction

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ABSTRACT

Heart rate plays a major role in myocardial ischemia. A high heart rate increases myocardial performance and oxygen demand and reduces diastolic time. Ivabradine reduces heart rate by inhibiting the I_f current of sinoatrial-node cells. In contrast to beta-blockers, ivabradine has no negative inotropic and lusitropic effect for a comparable heart rate reduction. Consequently, diastolic duration is increased with ivabradine compared to beta-blockers. This has potential consequences on coronary blood flow since compression of the vasculature by the surrounding myocardium during systole impedes flow and coronary blood flow is mainly diastolic. Moreover, ivabradine does not unmask alpha-adrenergic vasoconstriction and, unlike beta-blockers, maintains coronary dilation during exercise. In comparison with beta-blockers, ivabradine increases coronary flow reserve and collateral perfusion promoting the development of coronary collaterals. Ivabradine attenuates myocardial ischemia and its consequences even in the absence of heart rate reduction, possibly through reduced formation of reactive oxygen species. In conclusion, ivabradine differs from other anti-anginal agents by improving coronary blood flow and by additional pleiotropic effects. These properties make ivabradine an effective anti-anginal and anti-ischemic agent for the treatment of patients with coronary artery disease.

1. Introduction

Stable angina pectoris is the most common manifestation of ischemic heart disease. Although the annual mortality rate is relatively low, with an annual incidence of non-fatal myocardial infarction between 0.5 [1] and 2.6% [2], anginal symptoms are often disabling. Obstructive atherosclerotic disease of the epicardial coronary arteries and dysfunction of the coronary microcirculation are the main pathogenetic mechanisms responsible for the reduction of coronary flow reserve (CFR) [3] and the initiation of myocardial ischemia under stress or exercise (Fig. 1).

Typically, ischemia and angina develop during conditions of increased cardiac workload due to the mismatch between oxygen demand and supply imposed by the limited CFR (Fig. 2).

The aims of treatment, which includes lifestyle changes, drugs and coronary revascularization by either percutaneous or surgical techniques, are to relieve anginal symptoms and improve quality of life. Drugs that attenuate anginal symptoms act mainly by improving the mismatch between oxygen demand and supply and include nitrates, beta-adrenoceptor and calcium channel blockers and potassium channel openers [4].

On a background of optimal medical therapy, revascularization by percutaneous coronary interventions (PCI) improves anginal symptoms [4]. However, in a substantial proportion of patients, the prevalence of angina at follow-up remains high despite successful revascularization. In the COURAGE trial more than 25% of patients were still experiencing angina 1 year after PCI, and at 5-year follow-up the incidence of angina was not significantly different from that in patients who did not undergo a revascularization procedure [5]. These findings suggest that, although revascularization is effective in removing coronary stenosis and its hemodynamic consequences, other mechanisms, including coronary microvascular dysfunction, contribute to the pathogenesis of ischemia and angina in these patients.

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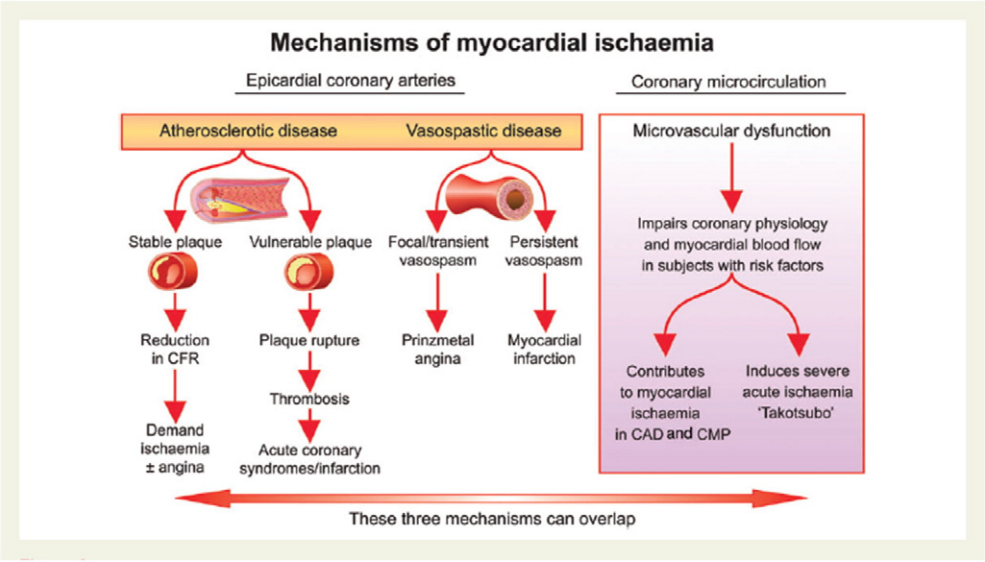

Fig. 1. Mechanisms of myocardial ischemia. In addition to the "classic mechanisms" of myocardial ischemia involving the epicardial arteries (i.e. atherosclerotic disease and vasospastic disease), coronary microvascular dysfunction (CMD) has recently emerged as an additional mechanism of myocardial ischemia. As in the case of the other two mechanisms, CMD (alone or in combination with the other two) can lead to transient myocardial ischemia as in patients with CAD or cardiomyopathy or to severe acute ischemia as observed in Takotsubo syndrome [3].

More recently, the sinus node inhibitor ivabradine, which reduces heart rate (HR) both at rest and during exercise, has been proven to have anti-anginal efficacy [6,7] and may be used in combination with beta blockers or as an alternative in patients who do not tolerate beta blockade [4]. Although the main anti-anginal mechanisms of ivabradine are reduction of myocardial oxygen consumption and improvement of coronary blood flow, more recent experimental and clinical investigations have demonstrated that ivabradine may reduce myocardial ischemia and its consequences not only through HR reduction, but also through additional pleiotropic mechanisms that contribute to improve coronary vascular and myocardial structure and function [8,9]. The aim of the present paper is to review the effects of ivabradine on coronary blood flow and ventricular function in patients with chronic ischemic heart disease.

2. Prolongation of diastolic duration and improvement of coronary blood flow at rest

The intramural coronary microvasculature is compressed by the contracting myocardium throughout systole such that almost no coronary blood flow occurs during systole. Thus coronary blood flow occurs mostly during diastole and, therefore, diastolic time is of major importance for a correct coronary physiology [10]. Beta-blockers and some calcium antagonists reduce HR decreasing myocardial oxygen demand while increasing diastolic time. The subendocardial left ventricular myocardium is particularly vulnerable to ischemia; an increase in diastolic duration and then in coronary blood flow is especially beneficial for subendocardial layers. In a normal heart, it has been estimated that a 1% increase of the diastolic time fraction increases the subendocardial flow by 2.6 to 6% [11]. Both the driving pressure gradient and the duration of diastole are integrated into the diastolic pressure–time integral, which is the essential mechanical determinant of coronary blood flow [12–14]. The effects of ivabradine and the beta-blocker atenolol on diastolic duration have been compared in dogs [15]. Ivabradine increased diastolic duration at rest and during exercise to a greater extent than atenolol, with similar HR reduction for both drugs [15]. As a result of the increased diastolic duration, ivabradine caused a greater increase in coronary blood flow for the same reduction in HR compared with atenolol.

A recently published randomized, double-blind, crossover study by Dillinger et al. [16] demonstrated an increase in diastolic duration with ivabradine in patients with coronary artery disease (CAD) receiving beta-blockers. Treatment with ivabradine over 3 weeks resulted in a 41% increase in diastolic duration and a 39% increase in the index of

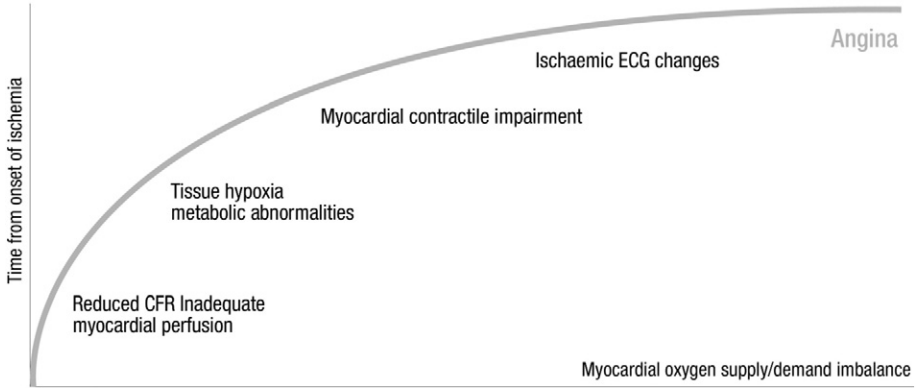

Fig. 2. The ischemic cascade. Temporal sequence of pathophysiological events initiated by an oxygen supply/demand imbalance.