

## Does nitric oxide mediate the effects of ivabradine in patients with heart failure?

Ivabradine is a pure heart rate-lowering agent and was recently approved for the treatment of heart failure (1). Ivabradine was approved for use in Europe by the European Medicines Agency for treating patients with heart failure with reduced ejection fraction of  $\leq 35\%$  and those with sinus rhythm with a resting heart rate (HR)  $\geq 75$  bpm because it was shown to confer a survival benefit in a subgroup analysis of this patient population (2). In the United States, there is a lower HR limit ( $\geq 70$  bpm) for ivabradine initiation (3).

Despite its clinical use, the precise mechanism of its beneficial action in patients with heart failure remains poorly understood. Animal studies have suggested that improved cardiomyocyte calcium handling (4, 5), reduced wall stress after myocardial infarction (MI) (5), improved coronary reserve due to reduced accumulation of perivascular collagen (6), improved diastolic compliance due to reduced fibrosis (7), and antiarrhythmic effects due to reduced pathological HCN4 expression in ventricular cardiomyocytes (8) play a role in the mechanism of action of ivabradine.

In this issue of *The Anatolian Journal of Cardiology*, the authors of a paper "Ivabradine promotes angiogenesis and reduces cardiac hypertrophy in mice with myocardial infarction" (9) demonstrate that ivabradine administered to mice for 4 weeks after MI improved left ventricular function, reduced hypertrophy, decreased cardiac fibrosis, and increased capillary density. This was accompanied by enhanced Akt-eNOS signaling and inhibited p38 mitogen-activated protein kinase (MAPK) activity. Therefore, they hypothesized that the beneficial effects of ivabradine therapy are associated with the activation of Akt-eNOS signaling.

Akt kinase phosphorylates multiple downstream substrates, including endothelial nitric oxide synthase (eNOS), that are involved in cell survival, proliferation, metabolism, and growth (10). Thus, Akt contributes to normal endothelial functions and its activation by vascular endothelial growth factor (VEGF) stimulates endothelial cell proliferation, migration, and survival (11) in a nitric oxide (NO)-dependent manner. Indeed, loss of Akt in mouse endothelial cells results in reduced NO release and impaired angiogenesis (12).

p38 MAPK is a potent trigger of cardiac hypertrophy (13). In the post-MI mouse model, Akt-eNOS activation by ivabradine

can also inhibit this pathway; however, indirect effects must also be considered. Better preservation of cardiac function can simply result in fewer stimuli for cardiac hypertrophy.

How does ivabradine stimulate Akt-eNOS signaling? Lei et al. (14) offer a potential explanation. They demonstrated that chronic bradycardia induced by alinidine in post-MI rats increased the expression of both VEGF and VEGF receptor, presumably via a stretch-activated mechanism. Therefore, it is possible that increased stretch related to lower HR and increased left ventricular diastolic filling could increase VEGF expression and thus trigger Akt-eNOS signaling. Therefore, NO can indeed be a mediator of the effects of ivabradine.

Obviously, there remain some unanswered questions. Do all heart rate-lowering agents (e.g. beta-blockers) have the same effects on Akt-eNOS signaling? Does this pathway mediate all the beneficial effects of ivabradine? Does it also operate in humans? Future studies are required to address these very important questions.

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