

**EDITORIAL COMMENT**

**Beta₃-Adrenoceptor Activation Just Says NO to Myocardial Reperfusion Injury**

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For the increasing number of patients who survive an acute myocardial infarction, infarct size is the main determinant of further prognosis (1). Timely reperfusion is mandatory to reduce infarct size, and for all conditioning strategies— ischemic pre-conditioning, delayed ischemic pre-conditioning, ischemic post-conditioning, and remote pre-conditioning— reperfusion is a prerequisite to reduce infarct size (i.e., they delay rather than ultimately prevent infarct development) (2). The pioneering experiments demonstrating reduction of infarct size by timely reperfusion are only 40 years old (3), and eventually was quickly translated to clinical use in patients with bolus initial and primary percutaneous intervention subsequently. However, the initial enthusiasm for all sorts of interventions to reduce infarct size soon gave way to a more sober and critical view (5).

The cardioprotective action of beta-blockade is largely attributed to antagonism of cardiac beta₁- and, to a lesser extent, beta₃-adrenoceptors and a resulting reduction of heart rate (15). More recently, a beta₃-adrenoceptor has been identified, also in humans (16). Nebivolol is not only an antagonist at beta₃-adrenoceptors but also an agonist at beta₃-adrenoceptors and induces NO formation through the endothelial and the inducible isoform of NOS (17,18). In this issue of the *Journal*, Aragón et al. (19) now report infarct size reduction by nebivolol, when given at the time of reperfusion (i.e., through attenuation of reperfusion injury) in a mouse model of 45-min coronary occlusion and 24-h activation of an intracellular proteolytic program. The mechanisms to protect from ischemia/reperfusion injury, which are recruited to a varying extent by the different conditioning strategies and by pharmacological agents, are equally complex and inter-related: there are 3 major receptor- and nonreceptor-activated intracellular signaling pathways (i.e., the endothelial nitric oxide [NO] synthase [eNOS]–protein kinase G pathway; the reperfusion injury salvage kinase [RISK] pathway comprising inositol-triphosphate [PI3]-kinase, protein kinase B, extracellular signal-regulated kinase, and glycogen synthase kinase-3-beta; and the survivor activating factor enhancement [SAFE] pathway comprising signal transducer and activator of transcription and sphingosine), which all converge onto the mitochondria as a decisive element for cardiomyocyte survival or death (8) (Fig. 1).

NO is causally involved in endogenous cardioprotection, and exogenous NO administration also protects from ischemia/reperfusion injury (8,9). Nitric oxide is part of the signal transduction of delayed ischemic pre-conditioning and of ischemic post-conditioning; its role in classical ischemic pre-conditioning is still somewhat contentious. NO also contributes to myocardial hibernation (10). NO is a central signaling element of the eNOS–protein kinase G pathway of cardioprotection but is also involved in a sideline of the reperfusion injury salvage kinase pathway and upstream of tumor necrosis factor-alpha in the survivor activating factor enhancement pathway (8). Endogenous NO originates from several cellular compartments in the heart (endothelium, cardiomyocyte, leukocyte) and from 3 NOS isoforms (endothelial NOS, inducible NOS, neuronal NOS) but is also formed non-enzymatically and/or through the reduction of nitrite by myoglobin during myocardial ischemia/reperfusion (11,12). Exogenous NO protects not only in experimental animals but also in humans (13). Apart from serving as a signal to activate guanylate cyclase, NO targets the mitochondria. NO induces mitochondrial ATP-dependent potassium channel-opening; also, at low concentrations, NO inhibits opening of the mitochondrial permeability transition pore (14), whereas at high levels it facilitates mitochondrial permeability transition pore opening. Reversible inhibition of mitochondrial complex I by S-nitrosation limits excess formation of reactive oxygen species during reperfusion (12).

Almost simultaneously with the benefits of reperfusion, the downside of reperfusion (i.e., reperfusion injury) was recognized (6). Reperfusion injury includes arrhythmias, reversible post-ischemic contractile dysfunction (stunning), microvascular no-reflow, and increased infarct size; the contribution of reperfusion to ultimate infarct size seemed paradoxical and was long debated but is now established after the recognition of the post-conditioning phenomenon (i.e., the reduction of infarct size by modified reperfusion) (7).

The mechanisms of reperfusion injury are complex and inter-related, including excess formation of reactive oxygen species, calcium overload, mitochondrial dysfunction, and

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reperfusion. The protection was associated with increased endothelial NOS phosphorylation, neuronal NOS expression, and myocardial nitrite and nitrosothiol concentrations. The protective action of nebivolol was shared by 2 more specific beta3-adrenergic receptor agonists, and it was abrogated in beta 3-adrenergic receptor-, endothelial NOS-, and neuronal NOS-knockout mice as well as by pharmacological inhibition of beta3-adrenergic receptors and NOS. Nebivolol when given shortly before myocardial ischemia also protected in a "pre-conditioning mode," apart from specific attenuation of reperfusion injury, but protection of pre-conditioning might also largely occur during early reperfusion (20).

Essential questions that remain open from the present study relate to details of the signaling cascade: "Activation of beta3-adrenergic receptors in which cellular compartment (endothelium, cardiomyocyte, neuron) is linked through which intermediate signaling steps to activation of which NOS isoform?" The present study provides evidence only for the involvement of the endothelial and the neuronal NOS isoforms, but nebivolol has also been demonstrated to increase the expression of the inducible NOS isoform, although that was after several hours of exposure (18).

Apart from providing details of the underlying signal cascade, the present study in an acute mouse model clearly advocates the use of nebivolol for acute cardioprotection. A critical issue for any cardioprotective intervention, however, is the translation to clinical use (21,22). There are major species differences in signal transduction (23); and age (24), comorbidities, and co-medications also contribute to the problem of translation (2,21). Therefore it would be important to confirm the present novel findings in a more clinically relevant model and ultimately in proof-of-concept clinical studies.

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