Vagal nerve stimulation protects the heart against myocardial ischemia-reperfusion injury

La estimulación vagal protege contra la lesión por isquemia-reperfusión

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Despite significant improvements in medical therapy, acute myocardial infarction (MI) is still the major contributor to mortality and morbidity worldwide. (1) Although timely reperfusion of the occluded coronary artery is necessary for salvage of cardiac cells and function, reperfusion of the jeopardized myocardium results in a cascade of harmful events, referred to as reperfusion injury. (2) In addition, reperfusion-injury itself contributes to the increase of myocardial infarction, and consequently plays a major role in the progression of adverse left ventricular remodeling as well as chronic heart failure. (3) Of importance, the treatment of heart failure patients represents a huge socioeconomic burden on individuals and health care systems. Therefore, there is need to identify novel clinically feasible, cost-effective intervention(s) and targets which reduce infarct size as well as the progression of adverse left ventricular remodeling.

Recent studies demonstrated that reduced parasympathetic activity and counterbalancing sympathetic hyperactivity in myocardial ischemia-reperfusion (IR) is associated with cell necrosis as well as contractile dysfunction. (4) In addition, there is considerable autonomic disturbance in heart failure; the excess of sympathetic activity and the withdrawal of vagal activity clearly contribute to the progression of ventricular remodeling as well as worse outcome of heart failure. (4) Therefore, therapeutic approaches acting on either reduced sympathetic hyperactivity or enhanced parasympathetic activity might represent novel strategies to reduce myocardial IR injury. Recent pioneering studies demonstrating a number of device-based neuromodulation interventions targeting specific aspects of autonomic imbalance (e.g. renal denervation, cardiac contractility modulation, spinal cord stimulation, and carotid sinus nerve and vagal nerve stimulation) are being actively investigated in experimental and clinical studies. (5)

Vagal nerve stimulation (VNS) is a promising novel therapeutic approach to enhance cardiac parasympathetic activity. The safety and efficacy of VNS for the treatment of epilepsy and depression are well established. (6). Preclinical studies have shown the benefit of VNS to improve LV function and reduce infarct size and mortality in a variety of animal models of myocardial IR and heart failure. (7, 8) These studies have demonstrated the pleiotropic effects of this therapy, involving heart rate lowering, reduction of inflammation and apoptosis as well as inhibition of sympathetic hyperactivity. There is evidence that stimulation of the vagal nerve releases acetylcholine (Ach) which acts on both muscarinic and nicotinic receptors, initiating cellular and subcellular signaling pathways associated with cardioprotection, such as activation of the Akt-GSK-3β protection pathway. (7) In addition, similarly to VNS, ischemic preconditioning, which is one of the most powerful cardioprotective phenomena, whereby brief cycles of ischemia to a coronary bed renders it less susceptible to subsequent IR-injury, releases Ach as well as ultimately reducing infarct size. (9)

Emerging evidence also points towards an immunomodulatory function of the vagal nerve in the regulation of cytokine production, termed the 'cholinergic anti-inflammatory pathway. (10) Recently, it was demonstrated that electrical VNS decreased serum and cardiac TNF-α in wild type mice, but not in alpha-7 nicotinic acetylcholine receptor (α7 nAChR) deficient mice, emphasizing that the cholinergic anti-inflammatory pathway is strictly dependent on α7 nACh. (11) Of additional interest is the finding that electrical VNS protects from myocardial and remote vascular injury following myocardial IR via a mechanism that involves activation of the α7 nAChR. (12)

Most of the studies above mentioned have investigated the potential effect of VNS, applied throughout the entire IR period to achieve maximal cardiovascular protection. There are controversial data on the efficacy of VNS in terms of 1) duration of the stimulation and 2) on the identification of the effects of ischemia and reperfusion regarding infarct size limitation. A recent study demonstrated that the infarct size limiting effect of VNS was abolished when VNS was started at the

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onset of reperfusion. (13) In contrast, Uitterdijk et al. (14) found.that VNS reduced infarct size when stimulation was started 5 min prior to the onset of reperfusion and continued until 15 min of reperfusion. Thus, the optimal time window for the beneficial effect of VNS seems to need clarification. Moreover, despite previous studies showing the benefit of VNS on limiting infarct size, there is a gap in our knowledge regarding the activation of muscarinic and/or nicotinic receptors by VNS applied prior ischemia to as well as at the onset of reperfusion.

In this issue of the Argentine Journal of Cardiology, Kelly et al. (15) demonstrated for the first time that a single short period (10 minutes) of vagus nerve stimulation applied either prior to ischemia or at the onset of reperfusion effectively and with similar magnitude reduced infarct size in a mice model of acute myocardial IR. Of importance, the cardioprotective mechanisms are different; while VNS applied prior to ischemia activates muscarinic signaling pathways, VNS applied at the onset of reperfusion depends on the activation of nicotinic receptors. This finding leads to the conclusion that infarct size reduction by VNS is mediated via different signalling pathways. Interestingly, similar to ischemic pre- or postconditoning, a short single period of VNS resulted in a robust cardioprotective effect. In a recent pioneering study, Basalay et al. (16) demonstrated that the infarct size limiting effect of remote ischemic conditioning requires intact vagal innervation of the visceral organs and recruitment of a GLP-1R-mediated signaling pathway via M3 muscarinic receptors. However, the authors of the present study focused on the mechanism only at the level of receptors and speculated on the downstream signaling pathways. Therefore, further studies are warranted to explore the potential downstream signaling pathways, e.g. the activation of Akt-GSK-3β and release of GLP-1, as well as the reduction of inflammation due to the application of VNS. Additionally, in contrast to previous studies, the authors did not observe beneficial effects of VNS on myocardial function, e.g. contractility parameters and left ventricular end-diastolic pressure. Thus, it would be interesting in the future to examine whether this is due to the short time of VNS application or to other mechanisms. Finally, in agreement with the authors VNS is not practical to be used clinically in patients with acute MI. However, the potency of cardioprotection resulting from a short period of VNS provides a useful tool to better understand the physiological basis of cardioprotection, as well as a novel therapeutic strategy to protect the heart against IR injury.

Conflicts of interest

None declared.
(See authors' conflicts of interest forms on the website/Supplementary material).

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