EDITORIAL

Vagus nerve stimulation increases the size of myocardial infarction in an experimental model. ¿Paradox or opportunity?

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"How wonderful that we have met with a paradox. Now we have some hope of making progress."
NIELS BOHR
R. Moore. "Niels Bohr, the man and the scientist", 1967

The vagus is the longest cranial nerve and innervates organs of the neck, thorax and abdomen. Its origin in the central nervous system is the brain stem. Specifically, the dorsal motor nucleus of the vagus and ambiguous nucleus represent the centers of origin of efferent nerve fibers. The dorsal motor nucleus of the vagus is the origin of visceromotor efferent component of the vagus. Traditionally, the vagus was considered as the parasympathetic efferent nerve but it is actually accepted that is a mixed nerve with 80% of sensory afferent fibers and 20% motor efferent fibers. The vagal efferences regulate heart function, however, the right and left vagus nerves differ in this respect. Indeed, the right vagus nerve innervates predominantly the sinusal node and consequently acts on the heart rate, while the left one innervates the atrioventricular node regulating cardiac contractile force as a function of preload and has less influence on the frequency. The body of sensory afferent cells lie in nodose and jugular ganglia and these are projected into the nucleus of the solitary tract. The direct and indirect projections from the nucleus of the solitary tract are widespread to the brain. The vagus nerve is composed mainly of C fibers in the Erlanger and Gasser's classification.

Vagus nerve stimulation (VNS) goes back to the nineteenth century. In 1883 Corning carried out for the first time electrical VNS, in 1938 Bailey and Bremer provoked cortical synchrony by VNS, in 1949 Maclean and Pribram carried out VNS in anesthetized monkeys, in 1951 Dell and Olson in conscious cats, in 1980 Maclean studied the effects of VNS in CNS activity, in 1985 Zabara verified the attenuation of seizures in dogs and in 1988, Penry implanted a device for VNS in humans.

The use of VNS for epilepsy treatment was approved in Europe in 1994, and in the United States in 1997. In 1998 Baylor described the antidepressant effects of VNS and in 2001 the FDA approved the carrying out of clinical trials of VNS for the treatment of depression. Currently it is proposed that chronic VNS could be a potential treatment for many clinical conditions such as epilepsy, depression, anxiety, cognitive disorders and Alzheimer's disease, migraine, involuntary movements and other neuropsychic disorders. There is evidence to suggest that changes in brain function caused by VNS are mainly due to direct afferences rather than indirect effects mediated by its efferent projections (1).

In the cardiovascular area, numerous basic and clinical studies demonstrate the importance of autonomic interactions, mediated in part by the vagus nerve, so much in normal physiology of the heart as pathological. (2.3) (Figure 1) Indeed, the autonomic sympathetic and parasympathetic nervous system function in a reciprocal way: an increase in the activity of a component causes or provokes a decrease in the activity of the other. A level of neuroeffector interactions, the release of noradrenaline from sympathetic nervous terminals inhibits the release of acetylcholine from nearby vagal fibers, while preventing acetylcholine release of noradrenaline. The autonomic nervous system dysfunction contributes to the pathogenesis of more important cardiovascular diseases, including heart disease, hypertension, congestive heart failure, life-threatening arrhythmias and sudden death. Autonomic imbalances are correlated with the severity of heart disease, with marked sympathetic activation and abnormally low levels of parasympathetic activity. The sympathetic excitation shortens the refractory period of ventricles, reduces ventricular fibrillation threshold and produces peripheral and coronary vasoconstriction. Drugs that reduce cardiovascular sympathetic stimulation as the ß-blockers, are essential in the treatment of cardiac patients. (4) Moreover, chronic VNS, as treatment for heart failure, is currently under clinical investigation (5). Notably, recent experimental studies verify the beneficial effect of VNS in the absence of changes in heart rate. Independent vagal effects of the effect on heart rate include, among others, the antiadrenergic effect due to sympathetic-parasympathetic interaction, antiapoptotic effects (modulation of receptor of tumor necrosis factor), increase nitric oxide, reduction of damage by ischemia and reperfusion (inhibition of mitochondrial polar opening) and 'inflammatory reflex' (6-9) Moreover, VNS induces inhibitor of metalloproteinase-1 and triggers the release of neuropeptides such as somatostatin, galanin, vasoactive intestinal peptide (VIP) and VIP 'like'

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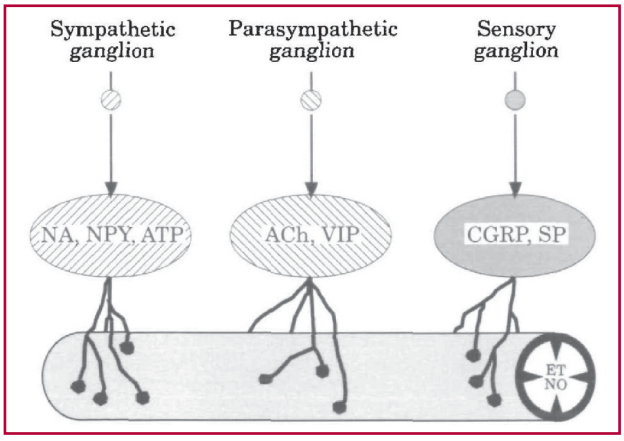

Table 1. Coronay vascular control by sympathetic, parasympathetic and sensory nerves and by endothetial cells that release endothelin and nitric oxide. (modified from 2) Ach = Acetylcholine, ATP = Adenosine Triphosphate, CGRP = Calcitonin Gene-Related Peptide, ET = Endothelin, NA = Noradrenaline, NPY = Neuropeptide Y, SP = Substance P, VIP = (poly)Vasoactive Intestinal Peptide.

(these latter regardless of blockage of muscarinic receptors and adrenergic ß). (10-13)

In this number of the Argentine Journal of Cardiology, Buchholz et al. verify, in an experimental model of ischemia in rabbits, that prior VNS, applied with the intention of inducing the release of acetylcholine, far to activate the mechanism of preconditioning and, consequently, reduce the ischemic area, infarct size increases and this effect is reversed with atropine or ß-blockers. (14) This finding is interpreted solely in light of the usual concepts about the interaction between sympathetic and parasympathetic system is, as the authors note, 'amazing.' On the one hand, the fact that infarct size is reduced with the administration of atropine evidences that muscarinic receptors play an important role. Similarly, the reduction of infarct size by administration ß blockers (ultrashort or long effect) reveales that activation of the sympathetic system would also play a significant role either by indirect stimulation or by the activation of α receptors or local release of neurotransmitters.

As Morisco et al. note in reference to cardiac hypertrophy, but whose concept may be extrapolated to other areas, 'the role of each molecular signal is not identical when they are studied using different stimuli. It is possible that the intensity and timing of expression of the molecule significantly affects its function in a given pathological condition'.(15) That is why, beyond using other models of cardiac ischemia, it seems necessary to corroborate the results of the work of Buchholz et al. modifying variables such as intensity, pulse width, frequency, duration of 'on' and 'off' periods and moment of VNS.

In conclusion, the findings of the work of Buchholz et. al contradict traditional concepts of cardiac pathophysiology. That is why they provide an opportunity to make significant progress in understanding the pathophysiological phenomena so important for the clinic such as ischemia, reperfusion, preconditioning and autonomic activity.

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