The main role of vegetative nervous system in protection of the heart

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Therapeutic sympathetic ganglia block has been used for almost one hundred years already. And the method has already been part of treatment of coronary artery disease for 50 years. Over this period, we have shown its positive effects on endo/epicardial blood flow, reduction of the size of ischemic lesions due to sudden-onset ischemic events, elevated fibrillation threshold of malignant arrhythmias, and recently also the distinctly positive effect of the block on myocardial cell metabolism. It is thus appropriate to ask the question why the nature has developed such a mechanism from which we profit when blocking it? In the first place, we should explain some relationships and contexts from phylogenetic development.
Autonomic nervous system evolution was an adaptive response of physiological functions to an ever growing social pressure. According to polyvagal theory, the phylogenetic shift in nervous regulation with autonomic nervous system passed through three principal stages related to behavioral strategy. The first stage is characterized by the development of unmyelinated primitive visceral vagus that had the role of rationalizing metabolic activity. The second stage was characterized by the development of sympathetic innervation the role of which was to increase metabolic activity and prepare the organism for fight or flight. The third stage consisted in the myelination of the vagus to regulate cardiac output. The entire development of autonomic nervous system is also characterized by mutual interactions of autonomic nerves and other physiological systems that influence the regulation of stress response, including cerebral cortex, hypothalamic-pituitary-adrenal axis, neuropeptides – oxytocin, vasopressin, and immune system.
All this constitutes a relatively sophisticated system of control of acute stress situations. Its role, however, declines in chronic states.

Greatest advances in the therapy of cardiovascular diseases have been accomplished apparently paradoxically – through blocking the processes and regulation mechanisms responsible for maintaining homeostasis and proper function of the organism. What we have in mind is the inhibition of chronically hyperactivated processes the character of which is maladaptive when acting long-term.
The philosophy of evolution is namely based on the rule that, as part of phylogenesis, all regulation mechanisms serve the purpose to be of help to acutely endangered individuals, i.e. endangered by fight (e.g. acute bleeding) or temporarily adverse living conditions (e.g. those related to dehydration or starvation). On the contrary, chronically ill patients are eliminated as individuals without perspective by this phylogenetic pressure. It has been our civilization that has first opposed this law and looks after its own weakest links, i.e. chronically ill patients. There have been many regulation mechanisms developed during phylogenesis. Some of them have only served in the lowest animals and have stopped being used with further evolution, other mechanism have been functionally preserved in the *Homo sapiens* species to this day and are active even under totally changed conditions of "*Homo sedativus*", the sedentary man, or "*Homo obesus*", the obese man. It is precisely these non-physiological conditions that result in maladaptive activities of both basic regulators: the sympatho-adrenal and RAA systems.

The former is activated in acute stress, e.g. in fight or flight, while the activity of the latter sets in under long-term adverse conditions. Sympathetic nervous system activation is part of a physiological defence reaction, the forefront of which consists in vasoconstriction, increased contractility, acceleration of heart rate, activation of haemostasis, all these reactions aiming at the preservation of blood circulation. In addition, a whole range of metabolic changes is stimulated that increase the offer of readily usable sources of energy. All this results, when active short-term, in improved chances of survival. But when this heightened sympathetic tone lasts for extended periods of time under pathological conditions – e.g. in cardiac failure, diabetes, hypertension, atrial fibrillation, myocardial ischemia, or in stroke – this hyperactivation is clearly undesirable. Chronic vasoconstriction produces hypertension, increased sarcoplasmic calcium activity results in myocardial instability associated with the risk of arrhythmias. Parallel with this, there is activation of thrombocytes and increased levels of fibrinogen which, in turn, start up both primary and secondary haemostasis with subsequent thrombotic and thromboembolic complications, and stress-related activation of glycide and lipid metabolism induces a complex of undesirable changes leading to athero- and thrombogenesis.
In a rather similar way, short-term activation of the renin-angiotensin-aldosterone system is advantageous when facing acute threat – vasoconstriction and fluid and salt retention maintain sufficient blood pressure as well as supply to vitally important organs, activation of inflammatory processes enables early reparation of damaged tissues, and activation of haemostasis reduces the risk of bleeding. Here the view obtains as well that, under pathological conditions, such as hypertension, cardiac failure, diabetes, atrial fibrillation, or myocardial ischemia, the system is in a status of long-term activation and must be suppressed. The negative impact of chronically hyperactivated RAA axis manifests in a broad range of malignant changes. At the level of blood pressure regulation, retention of sodium and water is stimulated in the kidneys, induced both through angiotensin II (AII) and the mineralocorticoid effect of aldosterone. In addition, sensation of thirst is induced through the action of AII on cerebral osmoreceptors. Vasoconstriction is the immediate results of direct AII action on smooth muscles. Longer-lasting hyperstimulation of AII, however, results in endothelial dysfunction with failing vasodilatation mechanisms (there is reduced availability of nitrogen oxide in particular), followed later on by vascular wall remodelling due to connective tissue proliferation and muscular hypertrophy, contributing to long-term elevation of peripheral resistance and fixation of hypertension. The resulting rise in blood pressure is a combination of higher amounts of circulating fluid (the volume-dependent component) and excessive peripheral resistance due to vasoconstriction (the resistance component). The impact on metabolism is due to reduced insulin sensitivity with undesirable hyperinsulinaemia and facilitated cholesterol transport to tissues via LDL, and, last but not least, to increased oxidative stress in the vascular wall. Atherogenic effect of RAA hyperactivation is based not only on increased blood pressure and the metabolic effects, but also on the activation of a number of cytokines with mitogenic and anti-inflammatory action (IL-6 – interleukin 6, TGF- transforming growth factor, PDGF – platelet-derived growth factor and other) and vascular adhesive molecules or selectins. Equally important is also the induction of a pro-thrombotic state due not only to the activation of thrombocytes, but also inhibition of fibrinolysis (due to increased offer of the natural plasminogen activator inhibitor type 1 – PAI-1).

This means that both our unhealthy way of life with excessive stress, insufficient physical activity and obesity, and the whole range of most commonly occurring cardiovascular diseases (cardiac failure, hypertension, atrial fibrillation, CAD) as well as non-cardiovascular diseases (diabetes, a number of nephropathies and hepatopathies) are accompanied by undesirable stimulation of regulatory mechanisms, especially, however, of the sympatho-

adrenal system and RAA axis. This hyperactivity contributes to the development of hypertension, atherothrombosis, dysrhythmias (especially atrial fibrillation), diabetes (and its complications), nephropathies (particularly diabetic nephropathy) or liver steatosis. For these reasons both these systems need to be concurrently curbed. This explains the focus of our interest on a strategy of their suppression, and also the fact why pharmaceuticals from the group of RAA system inhibitors and sympatho-adrenal activation inhibitors are the most widely used medications in cardiology and one of the group with the most dynamic growth of consumption.

1. Gottlieb SS, McCarter RJ, Vogel RA. Effect of Beta-Blockade on Mortality among High-Risk and Low-Risk Patients after Myocardial Infarction.
2. Hoffman BB. Adrenoreceptor-blocking drugs. In: Katzung BG (ed). Clinical Pharmacology.
Norwalk, CT, Appleton and Lange, 1994: 131–146.
3. Chandrashekhar Y, Sen S, Anway R, Shuros A, Anand I. Long-Term caspase inhibition ameliorates apoptosis, reduces myocardial troponin-I cleavage, protects left ventricular function, and attenuates remodeling in rats with myocardial infarction. JACC, 2004; 43, 2: 295–301.
4. Kloner RA, Shook T, Antman EM, et al. Prospective temporal analysis of the onset of preinfarction angina versus outcome: An ancillary study in TIMI 9B. Circulation 1998; 97: 1042–1045.
5. Murray CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. Circulation 1986; 74: 1124–1136.
6. Pier D. Lambiase, Richard J. Edwards, Michael R. Cusack, Clifford A. Bucknall, Simon R. Redwood, Michael S. Marber Exercise-induced ischemia initiates the second window of protection in humans independent of collateral recruitment. JACC, 2003; 41, 7: 1174–1182.
7. Salpeter SR, Ormiston TM, Salpeter EE. (2002). Cardioselective β-Blockers in Patients with Reactive Airway Disease: A Meta-Analysis. Ann Intern Med, 2002; 137: 715–725.
8. Shinmura K, Kodani E, Xuan YT, Dawn B, Tang XL, Bolli R. Effect of aspirin on late preconditioning against myocardial stunning in conscious rabbits, JACC, 2003; 41, 7: 1183–1194.
9. Szwed H, Sadowski Z, Elikowski W, Koronkiewicz A, Mamcarz A, Orszulak W, Skibinska E, Szymczak K, Swiatek J, Winter M. Combination treatment in stable effort angina using trimetazidine and metoprolol. Results of a randomized, double-blind, multicentre study (TRIMPOL II). European Heart Journal, 2001; 22, 24: 2267–2274.
10. The CREATE-ECLA Trial Group Investigators. Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction. JAMA 2005; 293: 437–446.
11. Verma S, Fedak PWM, Weisel RD, Butany J, Rao V, Maitland A, Li RK, Dhillon B, Yau TM. Fundamentals of reperfusion injury for the clinical cardiologist. Circulation, 2002; 105: 2332–2336.
12. Wallhaus TR, Taylor M, DeGrado TR, et al. Myocardial free fatty acid and glucose use after carvedilol treatment in patients with congestive heart failure. Circulation, 2001; 103, 20: 2441–2446.
13. Yusuf S. Two decades of progress in preventing vascular disease Lancet, 2002; 360, 9326: 2–3.