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Transcutaneous vagus nerve stimulation attenuates cardiac remodeling in a rat model of heart failure with preserved ejection fraction

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Background: Heart failure with preserved ejection fraction (HFpEF) has become a major public health concern and, so far, no treatment has been shown to decrease morbidity or mortality. Recent animal and human studies support the notion that pro-inflammatory and pro-fibrotic stimuli play a central role in the development of HFpEF. We have previously shown that transcutaneous vagus nerve stimulation (tVNS) is anti-inflammatory.
Purpose: We examined the effects of short-term intermittent tVNS on cardiac function, inflammation and fibrosis in a rat model of HFpEF.
Methods: Forty-eight Dahl salt-sensitive (DS) rats were randomized to 3 groups: low salt (0.3% NaCl; n=12) and high salt (4% NaCl) with either active tVNS (n=18) or sham tVNS (n=18) starting at 7 weeks of age. After 6 weeks of either low or high salt diet, sham or active tVNS was implemented for 30 minutes daily for 4 weeks. tVNS (20Hz, 0.2ms, 3mA) was accomplished by placing two oppositely charged magnetic electrodes over the auricular concha region, inside and outside, respectively, at each ear. In the sham tVNS group, the electrodes were placed on the auricular margin, which is devoid of vagus innervation. Echocardiography was performed at baseline and 4 weeks after treatment (endpoint) to assess cardiac function. Blood was collected at the same time points for cytokine analysis. Animals were euthanized at the end of the experiment and the left ventricle was examined for fibrosis.
Results: After 6 weeks of high salt diet, rats developed hypertension and left ventricular hypertrophy compared to low salt rats (129.4±14.6 mmHg vs. 114.1±17.4 mmHg; p=0.03 and 2.3±0.2 mm vs. 2.0±0.1 mm; p=0.001, respectively). tVNS attenuated the increase in blood pressure after 4 weeks of treatment (124.1±5.2 mmHg vs. 158.0±5.0; p=0.001). In addition, tVNS prevented the deterioration of diastolic function compared to sham stimulation (E/A ratio: 1.4±0.1 vs. 1.6±0.1, p=0.005; E/e' ratio: 8.1±0.5 vs. 11.1±0.5, p=0.001) and improved circumferential strain (-24.1±1.0% vs. -19.7±1.0%, p=0.002), without a change in left ventricular ejection fraction. Serum cytokines were not elevated in either group. Left ventricular fibrosis was decreased in the tVNS group compared to the sham group (2.5±1.2% vs. 4.1±2.2%, p=0.02) to the levels seen in the low salt rats (2.3±1.5%). Gene expression analysis of the left ventricle by qPCR showed up-regulation of pro-inflammatory and pro-fibrotic genes in the high salt sham group, compared to low salt rats, an effect which was reversed by tVNS.
Conclusion: These data indicate that tVNS ameliorates diastolic dysfunction and prevents cardiac remodeling in hypertensive rats by attenuating fibrosis and inflammation, thus suggesting that such a treatment may be used chronically to improve diastolic function in patients with HFpEF. Further studies to examine the efficacy of this novel treatment in patients with HFpEF are warranted.
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Disease management programs in Austrian heart failure patients

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Background: Nowadays there are multiple ways to improve the prognosis of heart failure including pharmaco- and device therapy. Nevertheless, decompensated heart failure is still frequent and hospitalization rates in patients with heart failure are high. To better control patients' well-being as well as their daily drug intake, Disease Management Programs (DMPs) have been developed and are recommended as class IA in the European Society of Cardiology heart failure guidelines. In Austria, discrepancies in the acceptance of DMPs have been observed which are, so far, not clarified. We hypothesized that patients in rural and urban regions may have different attitudes toward DMPs.
Methods: In a prospective study, patients hospitalized because of heart failure were asked by using a preset questionnaire comprising 40 questions about their opinion on DMPs and their knowledge and attitude about heart failure management. Two different groups were defined: one consisted of patients hospitalized in a rural area, the other comprised patients hospitalized in a big city. The survey results between the rural and urban patients were compared.
Results: Sixty patients (females n=26, mean age 76 years, range 40–94) were included, 30 each in a hospital in a rural area and in a big city. Significant differences between rural and urban patients were found regarding the acceptance of nurse-based DMPs (p-value= 0.029) which was higher among rural patients. The level of willingness to be included into a telenursing-based program was the same for both groups (p=0.441). Patients from rural areas tended to accept nurses more likely in their private surroundings than patients living in an urban environment (p=0.114). While the patients' knowledge of heart failure was similar in both population groups and overall adequate, their views on the current medical care varied: Only 22% of the rural patients would consult a specialist for the follow-up, whereas 37% of the urban patients would consult a specialist (p=0.005)
Conclusion: Nurse-based DMPs seem to be more accepted by patients from a rural area than by patients living in a big city. DMPs for urban patients have to be developed according to their special needs.

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Coated EPA:DHA 6:1 nanoparticles cause greater endothelium-dependent relaxations of coronary artery rings than the native form: role of NO, endothelium-dependent hyperpolarization and prostanoids

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Background: Omega 3 polyunsaturated fatty acids (PUFAs) containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have vasoprotective effects, in part, by stimulating the endothelial formation of the potent vasoprotective factor nitric oxide (NO) with EPA:DHA 6:1 being a superior formulation. Since PUFAs are highly unstable, the possibility that nanoencapsulation of omega 3 PUFAs followed by coating might enhance their stability and bioactivity remains to be determined.
Purpose: The aim of the present study was to develop coated EPA:DHA 6:1 nanoparticles, characterize their stability and evaluate their ability to cause endothelium-dependent relaxations of isolated coronary arteries, and to determine the underlying mechanism.
Methods: EPA:DHA 6:1 was emulsified in water phase using phosphatidylcholine and other surfactants, and then coated with proteins and gum derivatives to increase the stability and dispersibility of the coated omega 3 nanoparticles emulsion. Changes in isometric tension of porcine coronary artery rings were determined using organ chambers. The role of NO was assessed using NG-nitro L-arginine (L-NA, NO synthase inhibitor), prostanoids using indomethacin (Indo, cyclooxygenases inhibitor), and endothelium-derived hyperpolarization (EDH) using TRAM-34 and UCL-1684 (calcium-dependent potassium channel inhibitors).
Results: The emulsification and coating protocols resulted in stable encapsulated EPA:DHA 6:1 particles with a particle size of 287.8 nm and a particle distribution size (PDI) of 0.107, which were similar after storage for 7 days at room temperature (particle size of 293.4 nm with a PDI value of 0.215) demonstrating the absence of leakage from particles. The coated EPA:DHA 6:1 nanoparticles caused greater endothelium-dependent relaxations than the non-formulated EPA:DHA 6:1 whereas at higher concentrations both preparations caused endothelium-independent relaxations. The endothelium-dependent relaxation to the coated EPA:DHA 6:1 nanoparticles was significantly inhibited by L-NA and not affected by indo, and TRAM-34 and UCL-1684. In contrast, the endothelium-dependent relaxation to the non-formulated EPA:DHA 6:1 was inhibited by L-NA, Indo and by TRAM-34 and UCL-1684.
Conclusion: Coated EPA:DHA 6:1 nanoparticles have a greater ability to cause endothelium-dependent relaxations by stimulating predominantly the endothelial formation of NO whereas the response to the non-formulated EPA:DHA 6:1 involves NO, EDH and vasorelaxant prostanoids. Thus, coating of omega 3 PUFA particles appears to be an attractive approach to enhance the vasoprotective effect of omega 3 PUFAs.

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Vascular function is negatively regulated by endothelial p53 in hyperglycemic and hypoxic conditions

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p53 is a tumor suppressor gene contributing for genomic stability. p53 is involved in a broad range of cellular responses including cellular senescence, thereby mediates undesirable responses in some settings in age-related disorders. Recently it was shown that p53 promotes pathologies in age-related diseases including diabetes and heart failure. Here we show that endothelial p53 induces vascular dysfunction in hyperglycemia and ischemic conditions. First, we generated streptozotocin (STZ) -induced murine type I diabetic model. In these mice, endothelial p53 expression was increased and acetylcholine-induced vasodilatation was significantly impaired. Endothelial cell specific p53 depletion significantly improved endothelial dysfunction in hyperglycemic condition. Further, p53 negatively regulated the phosphorylation of eNOS (p-eNOS) by up-regulating PTEN expression. We also found that p53 expression was increased in ischemic arteries. Endothelial cell specific p53 knockdown significantly augmented ischemia-induced angiogenesis. Next, we generated endothelial cell specific MDM4 knockout (EC-MDM4 KO) mice. EC-MDM4 KO mice increased p53 expression and decreased phospho-eNOS level in endothelial cells. Gain of function model of endothelial p53 resulted in endothelial dysfunction together with reduced angiogenesis in ischemic arteries. These results suggest that endothelial p53 is critically involved in regulating vascular function under hyperglycemic and hypoxic conditions. Suppression of endothelial p53 would become a novel therapeutic target for metabolic diseases.