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**Chronic therapy with electric Vagus Nerve stimulation normalizes mRNA and protein expression of nitric oxide synthase in myocardium of dogs with heart failure**

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**Background:** Endothelial nitric oxide synthase (eNOS) is decreased in heart failure (HF), a maladaptation that leads to the release of pro-inflammatory cytokines and to cardiomyocytes apoptosis. Neuronal NOS (nNOS) and inducible NOS (iNOS) are increased in HF. The latter is partly responsible for the reduced responsiveness of the failing myocardium to exogenous catecholamines. We previously showed that chronic (3 months) therapy with electric Vagus nerve stimulation (VNS) using the CardioFit System (BioControl Medical, Ltd.), improves LV function in dogs with microembolization-induced HF. This study examined the effects of VNS on mRNA and protein expression of eNOS, iNOS and nNOS and the nitrate + nitrite pool (NNP = end product of nitric oxide, NO) in LV myocardium of VNS-treated HF dogs. **Methods:** RNA was extracted and homogenate was prepared from LV tissue of 7 VNS-treated dogs, 6 HF control dogs and 6 normal (NL) dogs. mRNA expression of eNOS, iNOS, and nNOS was measured using reverse transcriptase polymerase chain reaction and protein expression was measured by Western blotting. Bands were quantified in densitometric units (du). **Results:** The data are shown in the table. mRNA and protein expression of eNOS decreased and that of iNOS and nNOS increased significantly in HF-controls compared to NL. VNS therapy normalized mRNA and protein expression of all 3 NOS subtypes. NNP decreased in HF-controls compared to NL ( $32 \pm 3$  vs.  $57 \pm 2$  pmols/gram,  $p < 0.05$ ) and significantly increased with VNS therapy ( $41 \pm 2$  pmols/gram) compared to HF-controls ( $p < 0.05$ ). **Conclusions:** Long-term VNS therapy with CardioFit normalizes mRNA and protein expression of NOS in LV myocardium of dogs with HF and enhances NO production. This finding may explain, in part, the observed improvement in LV function in HF dogs chronically treated with VNS.

	NL	HF-Controls	HF + VNS
eNOS mRNA (du)	$1.44 \pm 0.15$	$0.51 \pm 0.02^*$	$0.90 \pm 0.03^\dagger$
eNOS Protein (du)	$74.2 \pm 5.0$	$24.8 \pm 3.0^*$	$58.3 \pm 4.0^\dagger$
iNOS mRNA (du)	$1.68 \pm 0.15$	$4.05 \pm 0.14^*$	$2.69 \pm 0.28^\dagger$
iNOS Protein (du)	$6.6 \pm 0.6$	$29.7 \pm 1.3^*$	$8.4 \pm 0.4^\dagger$
nNOS mRNA (du)	$1.55 \pm 0.11$	$4.41 \pm 0.52^*$	$1.98 \pm 0.20^\dagger$
nNOS Protein (du)	$10.4 \pm 0.4$	$60.3 \pm 2.4^*$	$19.5 \pm 0.9^\dagger$

\*= $p < 0.05$  vs. NL; †= $p < 0.05$  vs. HF-Controls