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Long-term therapy with elamipretide normalizes activation of the mitochondrial signal transducer and activator of transcription 3 (mstat3) in of left ventricular myocardium of dogs with chronic heart failure

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LONG-TERM THERAPY WITH ELAMIPRETIDE NORMALIZES ACTIVATION OF THE MITOCHONDRIAL SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION 3 (MSTAT3) IN OF LEFT VENTRICULAR MYOCARDIUM OF DOGS WITH CHRONIC HEART FAILURE

Poster Contributions
Poster Hall, Hall C
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Session Title: Heart Failure and Cardiomyopathies: Heart Failure Is Just a Revolving Door
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Introduction: The signal transducer and activator of transcription 3 (STAT3) has been identified in mitochondria (MITO) of cardiomyocytes (mSTAT3). In STAT3 -/- cells, the activities of MITO complexes I and II of the electron transport chain (ETC) were reduced suggesting that mSTAT3 is required for optimal ETC function. Deactivation of STAT3, equated with dephosphorylation of tyrosine residues, has been shown to adversely impacted MITO respiration and, consequently, oxidative phosphorylation. We previously showed that long-term (3 months) therapy with elamipretide (ELAM, previously referred to as *BendaviaTM, MTP131 or SS31*), a novel MITO-targeting peptide, improves LV function and normalizes MITO respiration and rate of ATP synthesis in MITO of LV myocardium of dogs with heart failure (HF).

Hypothesis: This study tested the hypothesis that phosphorylation of mSTAT3 (mpSTAT3) is reduced in MITO of LV myocardium of HF dogs and is restored after long-term therapy with ELAM.

Methods: LV tissue was obtained from 14 dogs with microembolization-induced HF (LV ejection fraction ~30%) randomized to 3 months therapy with subcutaneous injections of ELA (0.5 mg/kg once daily, n=7) or saline (Control, n=7). LV tissue from 6 normal (NL) dogs was used for comparison. Protein levels of mSTAT3 and mpSTAT3 were determined in MITO fraction by Western blotting coupled with chemiluminiscence and band intensity was quantified in densitometric units (du).

Results: Protein level of mSTAT3 was 0.82±0.05 du in NL, decreased to 0.29±0.03 du in Controls ($p<0.05$vs. NL) and was normalized by ELAM (0.53±0.05 du, $p<0.05$ vs. Control). Protein level of mpSTAT3 was 0.71±0.08 du in NL, decreased to 0.13±0.02 du in Controls ($p<0.05$vs. NL) and was normalized by ELAM (0.39±0.04 du, $p<0.05$ vs. Control). The ratio mpSTAT3/mSTAT3 was 0.87±0.09 du in NL, decreased to 0.46±0.07 in Controls ($p<0.05$vs. NL) and was restored to near normal levels with ELAM (0.76±0.09, $p<0.05$ vs. Control).

Conclusions: mpSTAT3 level is reduced in MITO from LV of HF dogs and restored after chronic therapy with ELAM. Normalization of mpSTAT3 by ELAM likely contributed to be observed improvement in MITO function following therapy with ELAM in HF dogs.