Elamipretide Normalizes Protein and mRNA Expression Levels of Mitofilin in Left Ventricular Myocardium of Dogs with Advanced Heart Failure

H. N. Sabbah. R. C. Gupta. *Henry Ford Health System*, Detroit, MI

BACKGROUND

Mitofilin (MF) is a protein of the inner mitochondrial (MITO) membrane and has critical functions in MITO morphology and MITO fusion and fission and specifically in the formation of tubular cristae and cristae junctions. MF also regulates cytochrome c release during apoptosis. Down-regulation of MF results in increased apoptosis and disorganization of the MITO inner membrane; abnormalities that are also manifested in heart failure (HF). We showed that MF levels are markedly reduced in LV myocardium of dogs with HF as well as in explanted failed human hearts. Elamipretide (ELAM), a novel MITO-targeting peptide, has been shown to improve MITO function and morphology in animals with experimental HF.

PURPOSE

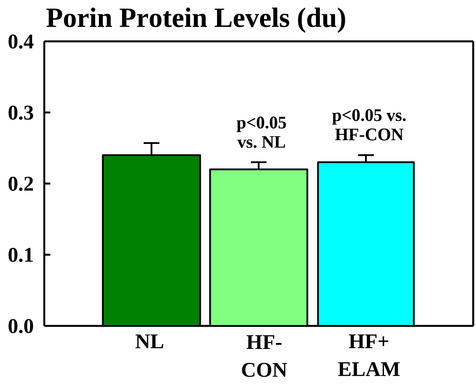
This study tested the hypothesis that chronic therapy with ELAM can reverse the dysregulation of MF in LV myocardium of dogs with coronary microembolization -induced chronic HF (LV ejection fraction ~30%).

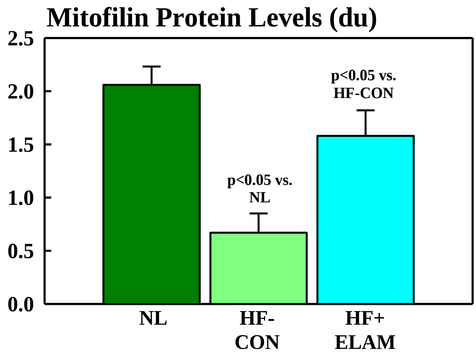
METHODS

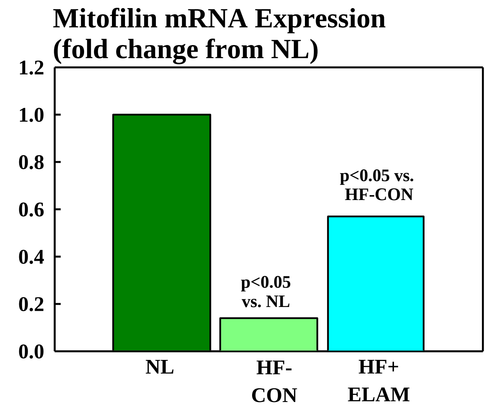
LV tissue from 14 HF dogs randomized to 3 months therapy with s.c. injections of ELAM (0.5 mg/kg once daily, n=7) or saline (control, CON, n=7) and tissue from 6 normal (NL) dogs was used in the study. Protein levels of MF and porin, an internal loading control, in LV tissue extracts were determined by Western blotting coupled with chemi-luminescence detection and band intensities expressed in densitometric units (du). Using specific primers, mRNA expression of MF normalized to GAPDH, an internal control, was measured in isolated RNA from LV tissue using real-time PCR and expressed as fold change from NL.

RESULTS

Porin and GAPDH levels were unchanged among the 3 study groups. Compared to NL dogs, levels of MF mRNA and protein were significantly reduced in HF-CON dogs. Therapy with ELAM restored both protein and mRNA expression to near NL levels.







CONCLUSION

Therapy with ELAM reversed the dysregulation of MF in LV myocardium of dogs with HF. The findings support the observation of improved MITO function and morphology observed in HF animal following chronic therapy with ELAM.

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