**USE OF THE NONIONIC BLOCK COPOLYMER, VEPOLOXAMER (P-188) FOR THE TREATMENT OF ADVANCED HEART FAILURE**

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Calcium overload occurs in cardiomyocytes (CMs) of the failing heart and contributes to cell death and progressive LV dysfunction. Vepoloxamer (VEPO), poloxamer-188, is a rheologic agent that can repair damaged cell membranes. We examined the effects of multiple acute infusions of VEPO on LV function in dogs with heart failure (HF) and tested the hypothesis that VEPO attenuates calcium overload by inhibiting unregulated calcium entry into failing CMs. 14 HF dogs were randomized to 2, 2 hrs infusions of VEPO (450 mg/kg, n=7) or saline (control, n=7) given 3 weeks (W) apart. LV ejection fraction and plasma troponin-I (TnI) were measured at baseline, at end of infusion and at 1 and 3W after each infusion. LV tissue was used to assess calcium ATPase activity (CaAA) and protein levels of phosphorylated (p) ryanodine receptors and p-sodium-calcium-exchanger-1 by Western blotting. Tissue from 7 normal (NL) dogs was used for comparisons. Separately, freshly isolated CMs from 6 HF-Control dogs were incubated for 2 hrs with VEPO or saline and then treated with 10 µM Fura-2 AM to flourometrically assess intracellular calcium. EF and TnI were unchanged in HF-Controls. VEPO increased EF and reduced TnI (\*=p<0.05 vs. control). CaAA was reduced and p-RYR-s2808 and p-NCX-1 levels increased in HF-Controls compared to NL. VEPO normalized all calcium cycling proteins and reduced intracellular calcium concentration. In conclusion, VEPO attenuated calcium overload in CMs and normalized calcium cycling resulting in lower TnI and improved LV function. The results support the development of VEPO for treating advanced HF.