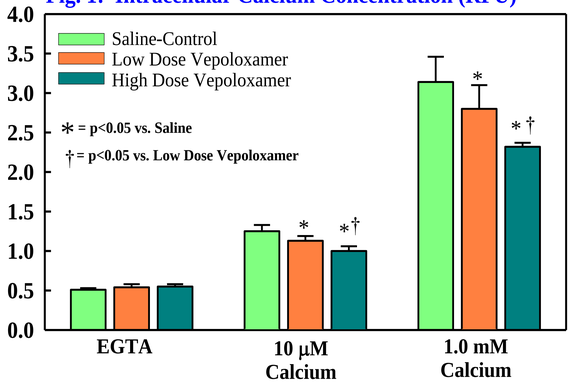
Effect of Repeat Intravenous Infusion of Vepoloxamer (Purified Poloxamer 188) on Left Ventricular Systolic Function in Dogs with Advanced Heart Failure

Hani N. Sabbah, , Mengjun Wang, Kefei Zhang, Ramesh C. Gupta, Henry Ford Hospital, Detroit, MI;
Marty Emanuele, Mast Therapeutics, Inc., San Diego, CA

INTRODUCTION

Calcium overload occurs in heart failure (HF) leading to cardiomyocyte dysfunction and death. Vepoloxamer (VEPO), purified poloxamer 188, is a rheologic agent that, in HF, has been suggested to improve microvascular blood flow and repair damaged cell membranes. The latter was recently shown to inhibit unregulated calcium entry into isolated cardiomyocytes (Fig. 1).

Fig. 1: Intracellular Calcium Concentration (RFU)



Presented HFSA Annual Meeting, Washington DC, September 26-29, 2015

OBJECTIVE

In this study, we examined the effects of repeat acute intravenous infusion of VEPO on LV function in dogs with microembolization-induced HF (LV ejection fraction, EF~30%).

METHODS

Fourteen HF dogs were randomized to 2 hour infusions of VEPO (450 mg/kg, n=7) or v/v normal saline (control, n=7). Each dog received 2 infusions of VEPO or saline administered 3 weeks apart. Dogs were followed for an additional 3 weeks after the second infusion (total follow-up 6 weeks). LV end-diastolic volume (EDV) and end-systolic volume (ESV), EF, and plasma n-terminal-pro brain natriuretic peptide (nt-pro BNP) were measured at baseline, at end of first infusion (2 hours), and at 24 hours (h), 1, 2 and 3 weeks (W) thereafter and then again at 24 hours (h), 1, 2 and 3 weeks (W) after the second infusion. The change between baseline and other study time points (treatment effect, Δ) was calculated.

RESULTS

Saline infusions had no effect on any of the examined functional measures. Compared to saline, VEPO reduced ESV (Fig. 2) and nt-pro BNP (Fig. 5) and increased EF (Fig. 4) without affecting EDV (Fig. 3), heart rate or mean aortic pressure. The benefits were sustained for at least 2 weeks after the first infusion of VEPO and up to 3 additional weeks after the second infusion of VEPO.

Fig. 2: Δ LV ESV (ml)

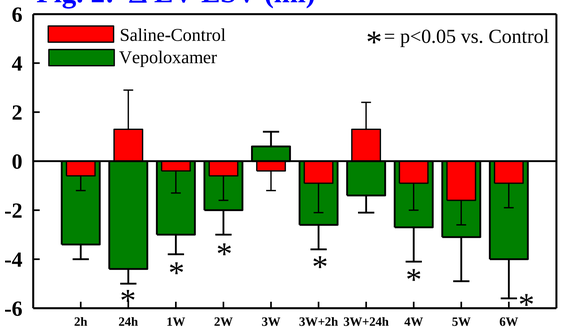


Fig. 3: Δ LV EDV (ml)

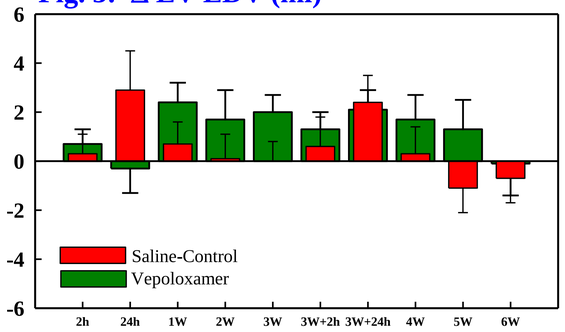


Fig. 4: Δ LV EF (%)

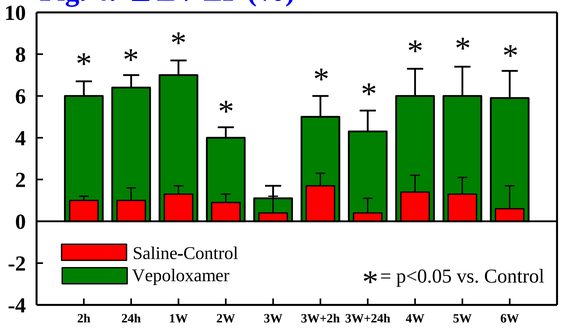
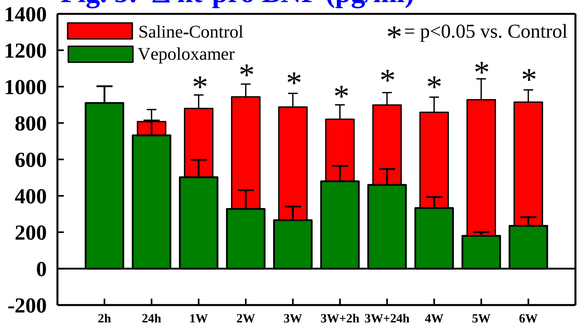


Fig. 5: Δ nt-pro BNP (pg/ml)



CONCLUSIONS

Therapy with repeat intravenous 2 hour infusions of VEPO, pulsed at 3 week intervals, elicit progressively sustained improvement in LV systolic function evident for at least 6 weeks. The results support development of VEPO for the treatment of acute HF and potentially for continued therapy post-hospital discharge for chronic HF.