Contribution of Nitric Oxide to vagal nerve function in the dystrophin deficient heart

M. Watson, E. Lee and A. Hoey, Centre for Systems Biology, University of Southern Queensland, Toowoomba, QLD 4350, Australia.

Duchenne muscular dystrophy (DMD) causes alterations in structure and function leading to cardiac failure. The lack of neuronal nitric oxide (NO) in the myocardium has been implicated in some of the cardiac pathologies seen in DMD. Neuronal NO has also been implicated in the control of the vagus nerve supplying the myocardium. The aim of the current study was to investigate the *in vivo* function of the vagus nerve in reducing heart rate (HR) in *mdx* mice and if alterations in NO signaling can modulate vagal nerve function.

Mice were anaesthetized with ketamine (100mg/kg) and xylazine (5 mg/kg) and the right vagus nerve exposed and stimulated at 1, 2 and 5 V at 1, 2, 5, 10 and 20 Hz. Electrocardiogram (ECG), heart rate (HR), heart rate variability (HRV) and cGMP levels were examined using an ELISA assay.

Young (12 week) and old (12 month) *mdx* mice had significantly elevated basal HR, while old *mdx* mice had prolonged QTc interval, a significant reduction in SDNN (standard deviation of N-N intervals) and in the high frequency (HF) domain. Young and old *mdx* mice had a significant reduction in the HR response to vagal nerve stimulation (VNS). 5% L-Arginine (w/v drinking water) and 25% isosorbide dinitrate (ISDN, 25% w/v water food) for four days had no effect on basal ECG parameters but significantly improved HRV. Furthermore, the response to HR reduction following VNS was significantly improved throughout the stimulation regimes. This was associated with an increase in the level of cGMP levels in the treatment groups. These results suggest that *mdx* mice have tachycardia and an impaired autonomic function while administration of compounds that elevate NO improve vagal nerve function.