

# ABSTRACT

## Nitric oxide can inhibit sympathetic outflow to the heart

We tested the hypothesis that the reduced heart rate response to sympathetic activation following exercise training is related to a peripheral sympathetic modulation of pacemaking by nitric oxide (NO). The effect of nitric oxide synthase (NOS) inhibition on the sympathetic control of heart rate was investigated in the isolated guinea pig double atrial/ right stellate ganglion preparation from exercise trained (6-weeks swimming) and sedentary animals.

The chronotropic response to sympathetic nerve stimulation expressed as a change in heart rate (bpm), significantly decreased in the exercise group (n=16) compared to the sedentary group (n=16) from  $30 \pm 5$  to  $17 \pm 3$  bpm, 1Hz ;  $67 \pm 7$  to  $47 \pm 4$  bpm, 3Hz ;  $85 \pm 9$  to  $63 \pm 4$  bpm, 5Hz and  $101 \pm 9$  to  $78 \pm 5$  bpm at 7 Hz stimulation ( $p < 0.05$ , un-paired t-test).

The chronotropic responses to bath applied noradrenaline ( $1 \times 10^{-7}$  M to  $1 \times 10^{-5}$  M) were not significantly different between exercise ( $EC_{50} 6.08 \pm 0.16$ , n=8) and sedentary groups ( $EC_{50} 6.18 \pm 0.07$ , n=7) demonstrating the  $\beta$ -adrenergic responsiveness was unaltered by physical training.

In the exercise group, the non-isoform selective NOS inhibitor, N- $\omega$  nitro-L-arginine (L-NA, 100  $\mu$ M) significantly increased the positive chronotropic response (bpm) to sympathetic nerve stimulation ( 3Hz, Control  $47 \pm 6$ , L-NA  $54 \pm 6$ , L-NA+L-arginine  $46 \pm 7$  bpm ; 5Hz, Control  $64 \pm 8$ , L-NA  $70 \pm 8$ , L-NA+L-arginine  $61 \pm 7$  bpm ,  $p < 0.05$ , one-way Anova). A similar trend that was not statistically significant was observed in the sedentary group. However, the positive chronotropic response to sympathetic nerve stimulation remained significantly attenuated in the exercise group compared to the sedentary group during NOS inhibition ( $P < 0.05$ , un-paired t-test).

A significant component of the reduced heart rate response to sympathetic nerve stimulation following training is mediated by a peripheral modulation of pacemaking. Our findings are consistent with the idea that a pre-synaptic mechanism alters neurotransmitter release or uptake and that the NO-pathway only plays a minor role in this response.