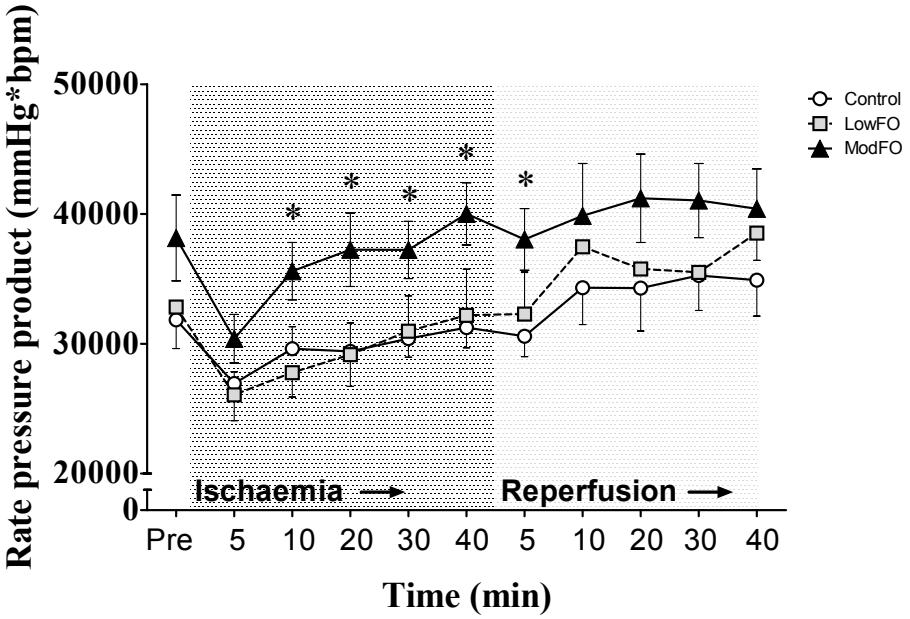
Cardiac *in vivo* haemodynamic function is modified by myocardial membrane DHA incorporation attributable to fish oil doses achievable in the human diet

M.J. Macartney, G.E. Peoples and P.L. McLennan, School of Medicine, University of Wollongong, Wollongong, NSW 2500, Australia.

Regular fish consumption is consistently associated with reduced cardiovascular disease rates in epidemiological and cohort studies, however RCT of supplements provide mixed results. Fish or fish oil (FO) intake increases myocardial membrane incorporation of long chain omega-3 polyunsaturated fatty acids (PUFA), particularly docosahexaenoic acid (DHA). Of physiological consequence, myocardial oxygen consumption is reduced without diminishing work output (Pepe *et al.*, 2002), early post-ischaemic contractile recovery is augmented (Pepe *et al.*, 2002) and infarct size is attenuated (Pepe *et al.*, 2002, 2007, Abdukeyum *et al.*, 2008) in the rat. However, previous animal studies have relied upon supra-therapeutical doses of FO, unachievable in the habitual human diet, and *ex vivo* experimental models to describe physiological changes. This study examined whether FO supplementation in the rat, using doses relevant to the human dietary range, are sufficient to modify *in vivo* cardiac haemodynamics under resting conditions and provide cardioprotection during ischaemia.

Male Sprague-Dawley rats (12-15w old, N=24) were fed isoenergetic diets (ad libitum 4w) containing 10% fat by weight (22% energy). The Control diet contained beef tallow (5.5%), n-6 PUFA sunflower seed oil (2.5%) and 2% olive oil (OO). High-DHA tuna FO (NuMega Lipids) was exchanged for OO to provide diets containing FO at 0.32% (LowFO) or 1.25% (ModFO) (Human equivalence: LowFO ≈ EPA+DHA 570mg/d, ModFO ≈ EPA+DHA 2.3g/d). Haemodynamic indices were measured under anaesthetic (pentobarbital: 60mg/kg i.p.) using a 6mm miniaturised 2-French pressure-volume conductance catheter during: rest; 45 min regional ischaemia induced by coronary artery occlusion; and post-ischaemic recovery. Fatty acid composition of left ventricular tissue was completed *via* gas chromatography.

Relative membrane fatty acid analysis confirmed that FO feeding increased myocardial membrane DHA incorporation (Control: 5.0±0.3, LowFO: 13.0±0.9, ModFO: 19.6±0.4%, $P<0.001$). Resting heart rate was reduced in a dose-related manner (Control: 453±6, LowFO: 433±4, ModFO: 402±5 beats.min^{-1}, $P=0.004$) with no compromise to cardiac output. Ischaemia-induced reductions in rate pressure product recovered faster in the ModFO group (data shown in the figure). Furthermore, post-ischaemic left ventricular pressure-volume loop integrity (shifted right with reduced ejection fraction in Control) was maintained in both FO groups. Zone at risk of infarction was not statistically different between groups (Control: 44±4.1, LowFO: 39±3.9. ModFO: 45±2.4%, $p>0.05$), indicating an equivalent ischaemic insult. These findings demonstrate that contractile dysfunction is modulated from FO doses in the human dietary range. The changes observed can be attributed to myocardial membrane DHA incorporation and highlight plausible and clinically relevant physiological changes that may contribute to the cardioprotective effects of regular fish consumption.



Mean±SEM; * $p < 0.05$ vs Control; n = 6 - 8 per group.