Is neonatal myocardial apoptosis a prelude to cardiac hypertrophy in the hypertrophic heart rat?

E.R. Porrello,[1,2] C.L. Curl,[1] S.B. Harrap,[1] W.G. Thomas[2] and L.M.D. Delbridge,[1] [1]Department of Physiology, The University of Melbourne, Parkville, Victoria 3010, Australia and [2]Baker Heart Research Institute, Prahran, Victoria 3004, Australia.

The mechanisms underlying neonatal programming of adult diseases remain elusive, but considerable attention has recently focussed on apoptosis as an antecedent of cellular hypertrophy. At maturity, the Hypertrophic Heart Rat (HHR) displays cardiomyocyte hypertrophy in association with an apparent reduction in myocyte number. The aim of this study was to establish a link between neonatal myocardial apoptosis and the developmental onset of cardiac hypertrophy in the HHR. Hearts were freshly isolated from euthanized (halothane anaesthesia) male HHR, and control strain Normal Heart Rats (NHR), at different stages of post-natal development (p2, 4wk, 6wk, 8wk, 12wk; n=8-11). Total cardiac weights were measured and divided by body mass to give a cardiac weight index (CWI, mg/g). Tissue bax-1 and bcl-2 mRNA expression levels were quantified in neonates by real-time RT-PCR to give a bax-1/bcl-2 ratio which was used as a 'cell death index'. At post-natal day 2, HHR hearts were considerably smaller than NHR (4.33±0.19 *vs* 5.01±0.08 mg/g, $p<0.05$). This growth-restricted phenotype was associated with a high bax-1/bcl-2 mRNA expression ratio in the heart (50% higher than NHR, $p<0.05$). HHR hearts 'caught-up' to NHR by 4 weeks (5.10±0.15 *vs* 5.16±0.11 mg/g) and were 11% larger than NHR by 8 weeks of age. This was followed by a rapid period of growth, and by 12 weeks of age HHR CWIs were 27% larger than NHR ($P(strain)<0.01$). Neonatal cardiac growth restriction, in association with increased expression of pro-apoptotic (or anti-survival) genes, is a prelude to cardiac hypertrophy at maturity in the HHR.