

**Neuregulin-1 improves cardiac function and clinical outcome in a juvenile rat model of right ventricular chronic pressure load.**

*Bossers G.P.L. (1), Van der Feen D.E. (1), Hagdorn Q.A.J. (1), Koop A.M.C. (1), Van Leusden T. (1), Borgdorff M.A.J. (1), Silljé H.H.W. (2), Berger R.M.F. (1), Bartelds B. (1)*  
*Center for Congenital Heart Diseases, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, The Netherlands (1); Department of Cardiology, University Medical Center Groningen, University of Groningen, The Netherlands (2)*

**Introduction:** Right ventricular (RV) pressure load (PL) plays a major role in the development of RV failure in congenital heart diseases (CHD). Recently, we revealed an increased proliferative potential in cardiomyocytes of rats with RV PL during childhood. Whether this improves adaptation is unknown. The aim of the present study was to test whether stimulation of proliferation can enhance RV adaptation to PL. We used Neuregulin-1 (NRG1), which is known to enhance proliferation through the ERBB2/4 pathway.

**Methods:** Rat pups (3 weeks old, 30-40 grams) were subjected to PL by means of pulmonary artery banding or sham at t=0 days. NRG1 or vehicle was administered to rats through intraperitoneal injection from t=3 until t=14 days and sacrificed at t=14, t=28 or t=56 days (young adulthood). We collected clinical symptoms of RV failure, including bodyweight, dyspnea, pleural effusion/ascites and cyanosis. Furthermore we performed analysis of functional and structural adaptation by means of sequential echocardiography and immunohistochemistry.

**Results:** NRG1 administration in sham animals did not affect hemodynamics or symptoms. Adequate pressure gradient was achieved in all PL rats. Treatment with NRG1 increased cardiomyocyte proliferation (Ki67) after 2 weeks. Treatment with NRG1 in rats with PL markedly postponed the development of clinical signs of RV failure. NRG1 treatment improved cardiac index ( $p < 0.05$  at 4 weeks,  $p = 0.06$  at 8 weeks).

**Conclusions:** In the present study we show that NRG1 administration in rats subjected to PL leads to increased cardiomyocyte proliferation during childhood, and this was associated with improved cardiac function and improved clinical outcome. These results support the hypothesis that cardiomyocyte proliferation can be a target as a cardioprotective strategy in children with diseased RV's in CHD.