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Dietary protein restriction throughout intrauterine development and postnatal life alters myocardial tissue composition but not left ventricular function in the adult mouse heart

Authors:
JD Drenckhahn¹, M Hennig², S Shimoyama³, L Ewering³, D Ewald², L Thierfelder², C Jux¹, ¹Justus Liebig University Giessen, Department of Pediatric Cardiology - Giessen - Germany, ²Max Delbrück Center for Molecular Medicine - Berlin - Germany, ³University Hospital Münster, Department of Pediatric Cardiology - Münster - Germany,

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Background - Protein restriction during intrauterine development in animal models induced by a maternal low protein diet (LPD) during pregnancy has been shown to reduce body and heart size in the offspring at birth. Such intrauterine growth restriction is proposed to negatively influence cardiac function and disease susceptibility in adulthood if animals are switched to a standard protein diet (SPD) after birth, a phenomenon referred to as developmental programming.

Purpose - We hypothesized that maintaining LPD conditions throughout intrauterine and postnatal life prevents pathological changes in the adult heart.

Methods – Female mice were subjected to LPD (containing 8.8% crude protein) during pre- and postnatal life and compared to age and sex matched controls constantly on SPD (22% crude protein). At the age of 11 weeks echocardiography, histological and molecular analyses were performed to evaluate heart function and myocardial tissue composition.

Results - Mice subjected to LPD exhibit a reduced body weight but normal heart weight and heart weight to body weight ratio compared to controls on SPD in early adulthood. Echocardiography measurements revealed minor changes in left ventricular (LV) morphology and normal contractility in LPD animals. Histological examination showed reduced interstitial fibrosis in the LV myocardium in LPD compared to SPD mice (0.65±0.1% vs. 1.06±0.09%, p=0.023), accompanied by normal expression of pro-fibrotic genes and extracellular matrix proteins. Expression of fetal genes reactivated in the adult heart in response to pathological conditions was not different between groups, largely excluding a negative impact of long-term LPD on the unchallenged heart in early adulthood. Surprisingly, we observed normal cardiomyocyte length but reduced cross sectional area resulting in a lower calculated cardiomyocyte volume (16406±1277 vs. 23776±1431 µm³, p=0.005) in LPD versus SPD hearts. Based on heart weight and cardiomyocyte volume we calculated the number of cardiomyocytes per heart, which was not different between groups (4.12±0.08 vs. 3.77±0.24 million). Instead, the number and proliferation rate of a non-myocyte cell population was increased in LPD compared to SPD myocardium (2523±191 vs. 1880±60 non-myocyte nuclei per mm² tissue, p=0.018).

Density of vimentin-positive fibroblasts and smooth muscle actin-positive myofibroblasts was reduced or unchanged in LPD hearts, raising the possibility that LPD conditions favor growth of another cardiac cell type, as for example cells forming the vasculature.

Conclusions - Pre- and postnatal dietary protein restriction in mice does not impair heart function under baseline conditions but alters cellular composition of the myocardium in adulthood. Identification of the underlying processes might have important implications for both developmental programming as well as the impact of diet composition on cardiovascular health and disease.