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CHRONIC KIDNEY DISEASE BONE DISEASE

MP345 CHRONIC KIDNEY DISEASE DISTURBS CARDIAC CALCIUM HANDLING DUE TO HIGH FGF23 LEVELSFGF23 LEVELS

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Introduction and Aims: The molecular changes that may underlie the increased prevalence of heart failure and cardiac mortality in CKD are ill-defined. Based on compelling epidemiological evidence linking FGF23 to uremic cardiomyopathy, we hypothesized that CKD directly impairs cardiac diastolic and systolic function due to FGF23-induced disturbances of calcium fluxes across the myocellular sarcoplasmic reticulum.
Methods: Seven weeks old C57Bl/6J mice were subjected to partial nephrectomy (5/6Nx) or sham-surgery, and after 6 weeks cardiac function was assessed using Cine MRI. In single intact cardiomyocytes diastolic and systolic function, as well as intracellular calcium transients were measured by fura-2 loaded cardiomyocytes. To examine whether an increased level of FGF23 is sufficient to achieve the cardiac phenotype observed in CKD, a second non-CKD group received either PBS or FGF23 i.p. injections for 7 consecutive days twice daily. mRNA expression of α-myosin heavy chain (α-MHC), β-myosin heavy chain (β-MHC) and atrial natriuretic factor (ANF) was determined by qPCR. Protein expression of total and phosphorylated phospholamban was quantified by Western blot.
Results: Although plasma cFGF23 levels were increased in 5/6Nx mice compared to sham mice (1.7-fold p=0.01), no difference was found for heart weight over tibia length and cardiomyocyte size, nor for ejection fraction, cardiac output, end diastolic and systolic volume, or E/A ratio. In addition, no difference in mRNA expression was found for cardiac hypertrophy markers ANF and α-MHC/β-MHC ratio between sham and 5/6Nx mice, which was comparable for PBS and FGF23 injected mice. In isolated cardiomyocytes, cytosolic calcium content in systole was decreased in 5/6Nx mice (-7.2%, p<0.001), which was mimicked by FGF23 injections (-11.6%, p<0.001). Compared to control, velocity of cytosolic calcium increase during systole was decreased in 5/6Nx mice and in mice receiving FGF23 injections (-16.2%, p<0.001 and -18.4%, p<0.05, respectively). In addition, the removal of calcium from cytosol during diastole was slower in 5/6Nx mice and this was again mimicked by FGF23 injections (-19.5%, p<0.001 and -22.2%, p<0.01, respectively). Protein expression of the ratio phosphorylated over total phospholamban could not explain these disturbed calcium fluxes, as it was not changed between groups, as shown by semiquantitative WB.
Conclusions: In the absence of CKD, FGF23 in isolation can mimic abnormal calcium fluxes seen in CKD cardiomyocytes. These molecular abnormalities precede the functional and structural cardiac abnormalities seen in longer-lasting CKD. Future studies need to identify the channelopathy causing these changed fluxes. FGF23 thus may serve as a new target to combat in CKD-related heart failure.