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

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On behalf of the NIGRAM consortium

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Introduction

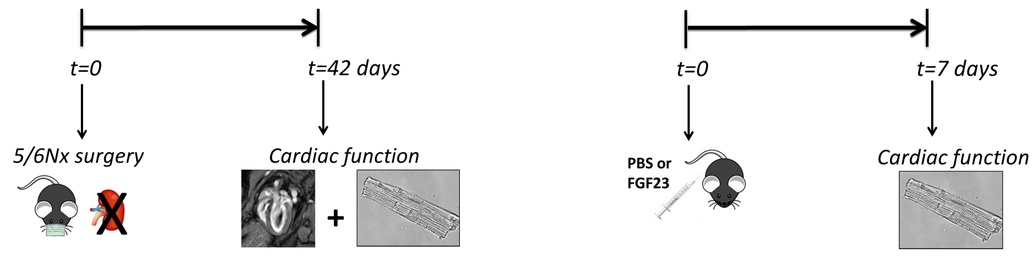
- Cardiovascular causes account for approximately 50% of mortality in patients with chronic kidney disease (CKD).
- The molecular changes that may underlie the increased prevalence of heart failure and cardiac mortality in CKD are ill-defined.

Hypothesis

- 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 male wild type C57Bl/6J mice were subjected to partial nephrectomy (5/6Nx) or sham-surgery and were kept in the study for six weeks.
- A second non-CKD group received either PBS or FGF23 i.p. injections for 7 consecutive days twice daily.
- *In vivo* cardiac function was assessed using Cine MRI
- In single intact cardiomyocytes *ex vivo* diastolic and systolic function, as well as intracellular calcium transients were measured by fura-2 loaded cardiomyocytes.
- 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.



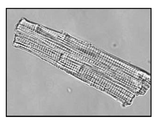
Results

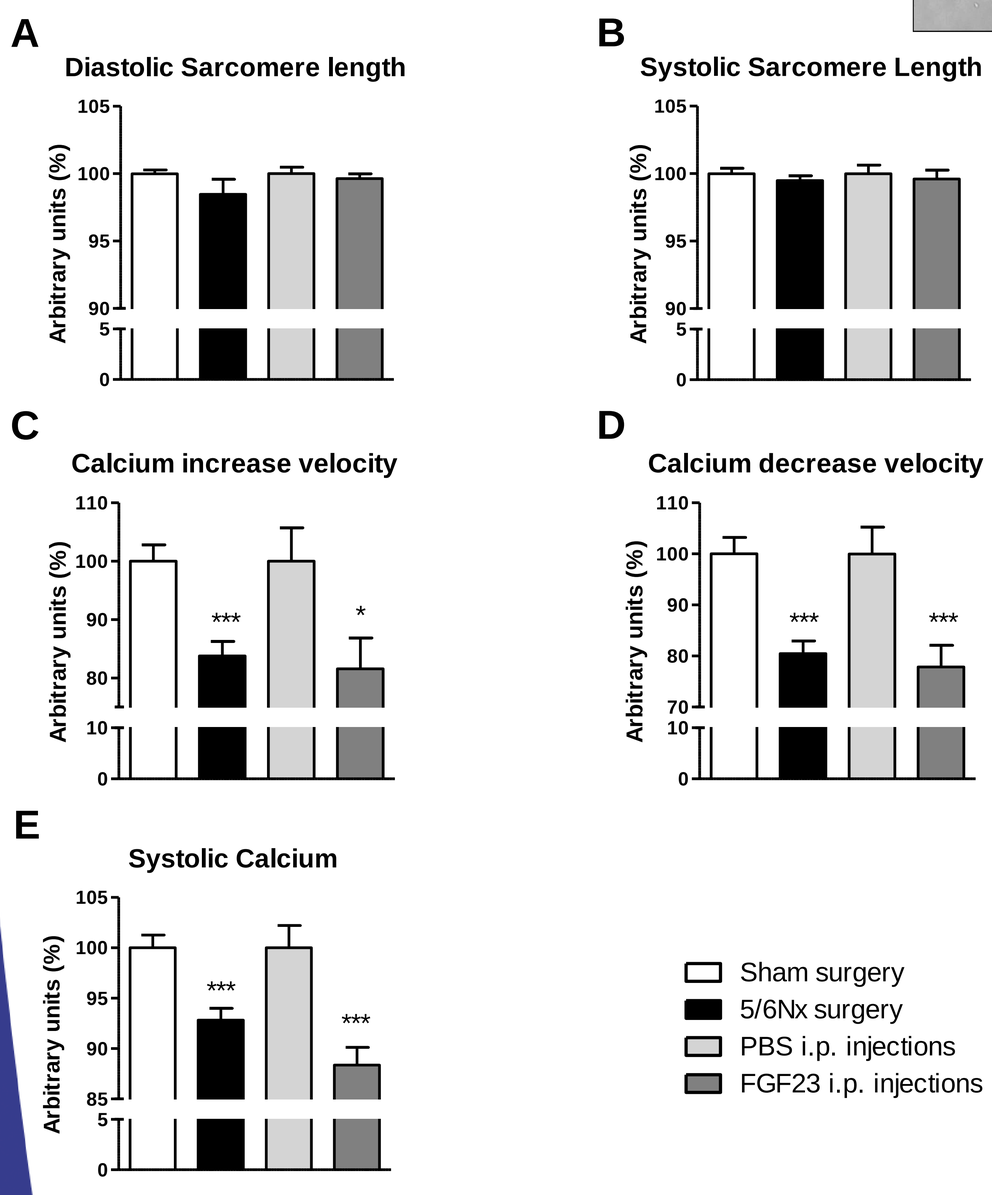
Table 1. 5/6Nx impairs kidney function and increases plasma FGF23 levels.

	Sham	5/6Nx	p-value
Plasma urea (mmol/L)	12.7 ± 0.3	22.1 ± 1.1	**<0.001**
Plasma creatinine (µmol/L)	15.0 ± 1.5	28.3 ± 1.6	**<0.001**
Urinary creatinine (µmol/24h)	2.62 ± 0.23	3.33 ± 0.15	**0.021**
Creatinine clearance (µl/min)	137.1 ± 20.4	92.8 ± 6.0	0.060
Plasma Ca^{2+} (mmol/L)	2.00 ± 0.02	2.17 ± 0.03	**0.001**
Urinary Ca^{2+} (µmol/24h)	1.07 ± 0.21	3.55 ± 0.31	**<0.001**
Plasma Pi (mmol/L)	3.37 ± 0.19	2.93 ± 0.12	0.088
Urinary Pi (µmol/24h)	19.2 ± 2.8	115.0 ± 18.4	**<0.001**
Fractional excretion phosphate (FEP) (%)	2.95 ± 0.92	17.01 ± 2.87	**0.003**
Plasma c-term FGF23 (pg/ml)	210.2 ± 13.1	315.2 ± 27.6	**0.002**
Plasma PTH (pg/ml)	255.6 ± 51.8	555.4 ± 83.8	**0.014**
Plasma 1,25-dihydroxyvitamin D_3 (pmol/L)	226.8 ± 10.2	252.6 ± 23.5	0.317

Data are mean ± SEM

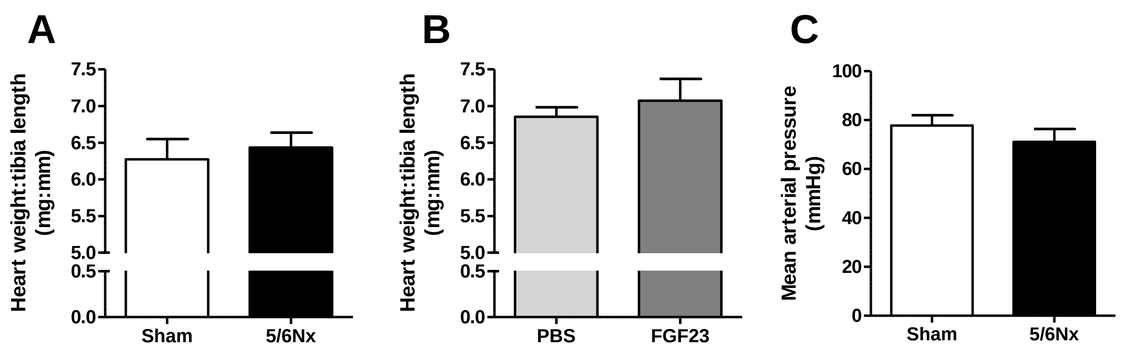
Figure 1. 5/6Nx impairs calcium fluxes in cardiomyocytes, which is mimicked by increasing circulating FGF23 levels.





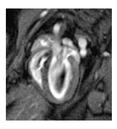
Data are mean ± SEM. *: p<0.05, ***: p<0.001 vs. sham or PBS.

Figure 2. 5/6Nx and FGF23 injections do not induce left ventricular hypertrophy (LVH).



Data are mean ± SEM.

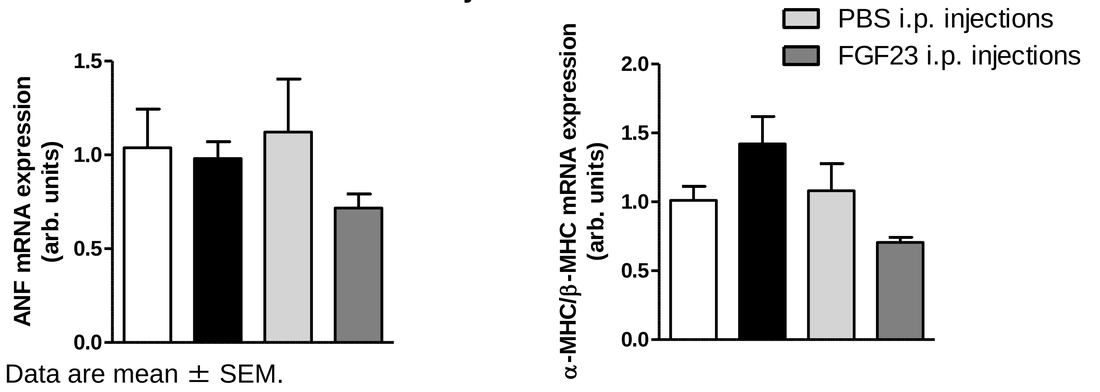
Table 2. Experimental renal failure does not induce impaired cardiac function measured by MRI.



	Sham	5/6Nx	p-value
Cardiac output (L/min)	4.80 ± 0.39	4.76 ± 0.25	0.886
Ejection fraction (%)	73.3 ± 1.6	72.4 ± 0.9	0.886
Stroke volume (µl)	43.9 ± 2.6	43.5 ± 1.9	1.000
End-systolic volume (µl)	16.4 ± 2.1	16.7 ± 1.1	0.886
End-diastolic volume (µ)	60.2 ± 4.6	60.2 ± 2.9	0.886
E/A ratio	1.39 ± 0.26	1.79 ± 0.20	0.182
Left ventricular mass (mg)	90.2 ± 3.3	91.54 ± 2.9	0.886

Data are mean ± SEM.

Figure 3. Gene expression markers of LVH are not altered after 5/6Nx and FGF23 injections.



Data are mean ± SEM.

Conclusions

- Chronic kidney disease disturbs cardiac calcium handling which can be explained by high FGF23 levels.
- These myocellular abnormalities precede the functional and structural cardiac abnormalities seen in longer-lasting CKD.
- FGF23 thus may serve as a new target to prevent CKD-related heart failure.

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53 ERA
Chronic Kidney Disease. Bone disease.
Melissa Verkaik
DOI: 10.3252/pso.eu.53era.2016
ePosters supported by F. Hoffmann- La Roche Ltd.
53rd CONGRESS ERA-EDTA VIENNA AUSTRIA MAY 21-24 2016
Held jointly with Österreichische Gesellschaft für Nephrologie
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