Chronic kidney disease disturbs cardiac calcium handling due to high FGF23 levels FGF23 levels


Published in: Nephrology Dialysis Transplantation

DOI: 10.1093/ndt/gfw190.02

Published: 01/05/2016

Document Version
Publisher’s PDF, also known as Version of Record (includes final page, issue and volume numbers)

Please check the document version of this publication:

- A submitted manuscript is the author's version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

Link to publication

Citation for published version (APA):
Verkaik, M., Oranje, M., Gam, Z., Abdurrachim, D., Prompers, J. J., Najafi, A., ..., Vervloet, M. G. (2016). Chronic kidney disease disturbs cardiac calcium handling due to high FGF23 levels FGF23 levels. Nephrology Dialysis Transplantation, 31(Supplement 1), i454. DOI: 10.1093/ndt/gfw190.02

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.
CHRONIC KIDNEY DISEASE BONE DISEASE

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

Melissa Verkaik1,2, Maarten Oranje1, Zeineb Gam1, Desiree Abdurrahim1, Jeanine J. Prompers3, Aref Najafi1, Diederik W. Kuster1, Manuella A.S. Al Sharkway1, Michiel Helmes1, Pieter M. ter Wee2, Jolanda van der Velden1, Etto C. Eringa1 and Marc G. Vervloet2

1VU University Medical Center, Department of Physiology, Institute of Cardiovascular Research ICaR-VU, Amsterdam, THE NETHERLANDS, 2VU University Medical Center, Department of Nephrology, Institute of Cardiovascular Research ICaR-VU, Amsterdam, THE NETHERLANDS, 3Eindhoven University of Technology, Department of Biomedical Engineering, Biomedical NMR, Eindhoven, THE NETHERLANDS

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.