Abstract: P3494

Fibroblast growth factor (FGF)-23 induces ventricular arrhythmogenesis through Ca2+ handling dysregulation

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Topic(s):
Cellular Biology - Excitation-contraction coupling and contractile remodelling

Citation:
European Heart Journal (2017) 38 (Supplement), 736

Funding Acknowledgements:
This work was supported by grants CP15/00129 from ISCIII, Fundación SENEFRO and Fondos FEDER

Introduction: Fibroblast growth factor (FGF)-23 is a hormone synthesized in bones in response of an increase in circulating phosphate levels. It is known that patients with chronic kidney disease (CKD) show high serum levels of FGF-23 and this increment is gradual as CKD progresses. Despite of FGF-23 has been classically associated to renal dysfunction, during the last years is also considered as a non-conventional risk factor of cardiovascular (CV) disease. However, it is completely unknown whether FGF-23 might alter cardiac contractile function, especially in advanced stages of renal disease in which circulating FGF-23 levels are strongly increased.

Purpose: 1) Analyze whether FGF-23 impairs calcium (Ca2+) handling, a key regulator of contractile function and consequently the ventricular rhythm. 2) Analyze the circulating levels of FGF-23 in dialysis patients and its relationship with the ventricular rhythm.

Methods: Enzymatically isolated adult rat ventricular myocytes (n=9) were perfused firstly with a vehicle solution and subsequently with a FGF-23 solution (100 ng/mL). L-type Ca2+ current (ICaL) was recorded by the whole-cell patch-clamp technique. Ca2+ handling and contractile function were analyzed using confocal microscopy. To determinate FGF-23-dependent pathways, cardiomyocytes were pre-incubated with the FGF-receptors inhibitor PD173074 (10 μmol/mL) or soluble klotho (s-klotho) (100 ng/mL). In addition, FGF-23 serum levels were measured by the FGF-23 (C-term) ELISA-kit in samples from patients under dialysis (n=52).

Results: FGF-23 induced a significant decline of ICaL (p<0.001), an important decrease in the intracellular Ca2+ transients amplitude (p<0.01) and in the sarcoplasmic reticulum Ca2+ load (p<0.01). All these alterations were functionally translated to a significant deterioration of cellular contraction values (p<0.01). Additionally, a considerable increase in diastolic Ca2+ sparks and waves (p<0.01) and therefore in the ryanodine receptors activity were observed during FGF-23 exposure. Interestingly, during FGF-23 perfusion cardiomyocytes showed a pro-arrhythmogenic phenotype when they were electrically stimulated. These effects induced by FGF-23 were blocked when cardiomyocytes were pretreated with PD173074 or s-klotho. On the other hand, serum levels of FGF-23 were strongly increased in dialysis patients, even reaching >1000 RU/mL of FGF-23 in 68% of total dialysis patients.
Conclusion: Our study uncovers FGF-23 as new target in the intracellular Ca2+ handling, able to impair contractile function and induce a pro-arrhythmogenic phenotype in adult cardiomyocytes.

Future perspectives: Alterations evoked by FGF-23 in cardiomyocytes could explain the CV events observed in patients with CKD, especially those in dialysis. The next step will be to analyze in CKD patients whether high FGF-23 levels impair cardiac function and heart rhythm.