THE KOREAN SOCIETY OF NEPHROLOGY
APCN & KSN 2024
June 13(Thu) - 16(Sun), 2024 Coex, Seoul, Korea
Promoting Sustainable Kidney Health: The Asia-Pacific and Beyond

Abstract Submission No.: A-1535

Myocardial hypertrophy and fibrosis are associated with tissue phosphorus accumulation, PIT1/ERK and progenitor cell regulatory molecule expression in mild CKD

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Objectives : The study was aimed to assess the early molecular and cellular features of myocardial remodeling in experimental CKD.
Methods : We induced CKD by 3/4 nephrectomy (Nx) in adult male spontaneously hypertensive rats (SHR) with a 4-month follow-up. Sham Wistar rats and SHR were controls. Animals were fed standard chow (0.6% phosphate). Myocardial phosphorus (P) content was assessed by inductively coupled plasma atomic emission spectroscopy (Saint Petersburg State University, Research Park). Parameters of chronic kidney injury and myocardial remodeling, serum levels of inorganic phosphate (Pi), PTH, and FGF23 were measured. Myocardial expression of phosphate transporters PiT1, ERK1/2 (Mapk3/1), calcineurin (Ppp3ca), Tgf-beta, nestin and Lgr4 were evaluated by PCR-RT, IHC and confocal microscopy (Pavlov Institute of Physiology, Center for Collective Use).
Results : Mild chronic kidney injury in Nx rats characterized with higher serum Pi and myocardial P content (Table 1). In combined SHR group Pi and P levels correlated directly with histological indices of intramyocardial arterial (IA) wall remodeling and myocardial IF. In Nx, higher cardiomyocyte diameter, myocardial interstitial and perivascular fibrosis were accompanied with upregulation in Ppp3ca ($p=0.007$) and Mapk1 mRNA ($p=0.046$), increase in phospho-ERK1/2 and PiT1 myocardium IHC-area (Table 1), nestin and Lgr4 expression in arterial wall (Figure 1b). PiT1 and pospho-ERK1/2 were co-expressed in IA media; nestin and LGR4 were expressed in IA adventitia and media, myocardial interstitium, and were co-localized occasionally (Figure 1 b).
Conclusions : Mild CKD is associated with histological and molecular features of cardiomyocyte hypertrophy, myocardial fibrosis and arterial remodeling, which are probably mediated by myocardium phosphate retention involving upregulation in PiT1/MAPK, and molecules related to progenitor cells proliferation and differentiation.

Table 1.jpg

Table 1 – Chronic kidney injury and phosphate exchange indexes, myocardial histology and morphometry in CKD and control groups

Parameter	Wistar	SHR	SHR Nx (mild CKD)	p-value (SHR vs. SHR Nx)
	Chronic kidney injury and phosphate exchange indexes			
Serum creatinine, µmol/L	74 (69;80)	77 (73;79)	93 (90;97) ↑	<0.001
Renal fibrosis, % blue Masson staining	2.8 (1.9;3.7)	3.7 (3.5;4.0)	9.7 (8.7;11.3) ↑	<0.001
Myocardium P content, mg/kg	--	425 (394;442)	496 (461;518)	0.027
Serum Pi, mmol/L	1.85 (1.72;1.96)	1.75 (1.61;1.98)	2.17 (2.05;2.26) ↑	0.002
Urinary Pi/Cr, mg/mg	6.1 (5.5;7.5)	8.3 (5.9;8.8)	9.7 (8.4;11.9)	0.07
PTH, ng/mL	74 (13;100)	49 (14;79)	136 (73;179)	0.08
FGF23, ng/mL	322 (220;936)	709 (391;756)	1879 (496;1252)	0.27
	Myocardial remodeling parameters, histology and morphometry			
Systolic blood pressure, mmHg	133 (127;140)	188 (180;195)	186 (180;190)	0.36
Myocardial mass index, g/kg	2.0 (1.9;2.2)	2.8 (2.3;3.0)	2.8 (2.7;3.2)	0.72
Cardiomyocyte diameter, mcm	14.0 (13.2;17.4)	18.0 (17.1;19.3)	22.3 (20.3;24.5) ↑	0.039
Myocardial interstitial fibrosis, % blue Masson staining	1.0 (0.5;1.4)	1.0 (0.7;2.7)	3.6 (2.5;7.0) ↑	0.042
Myocardial artery intima thickness, % artery diameter	3.0 (2.6;3.7)	3.9 (3.6;4.1)	4.5 (3.9;4.8)	0.25
Myocardial artery media thickness, % artery diameter	16.0 (14.5;16.8)	16.9 (16.5;17.4)	16.9 (16.5;17.3)	0.66
Myocardial artery adventitia thickness, % artery diameter	8.8 (8.0;11.0)	9.3 (8.3;11.5)	13.8 (13.4;14.3) ↑	0.005
Phospho-ERK1/2 IHC area, % wall	0.0 (0.0;1.0)	4.8 (0.0;10.0)	4.8 (2.2;9.3) ↑	0.011 (vs. Wistar)
PiT1 IHC area, % wall	50 (39;56)	59 (47;74)	67 (58;68) ↑	0.002 (vs. Wistar)

Table 1.jpg

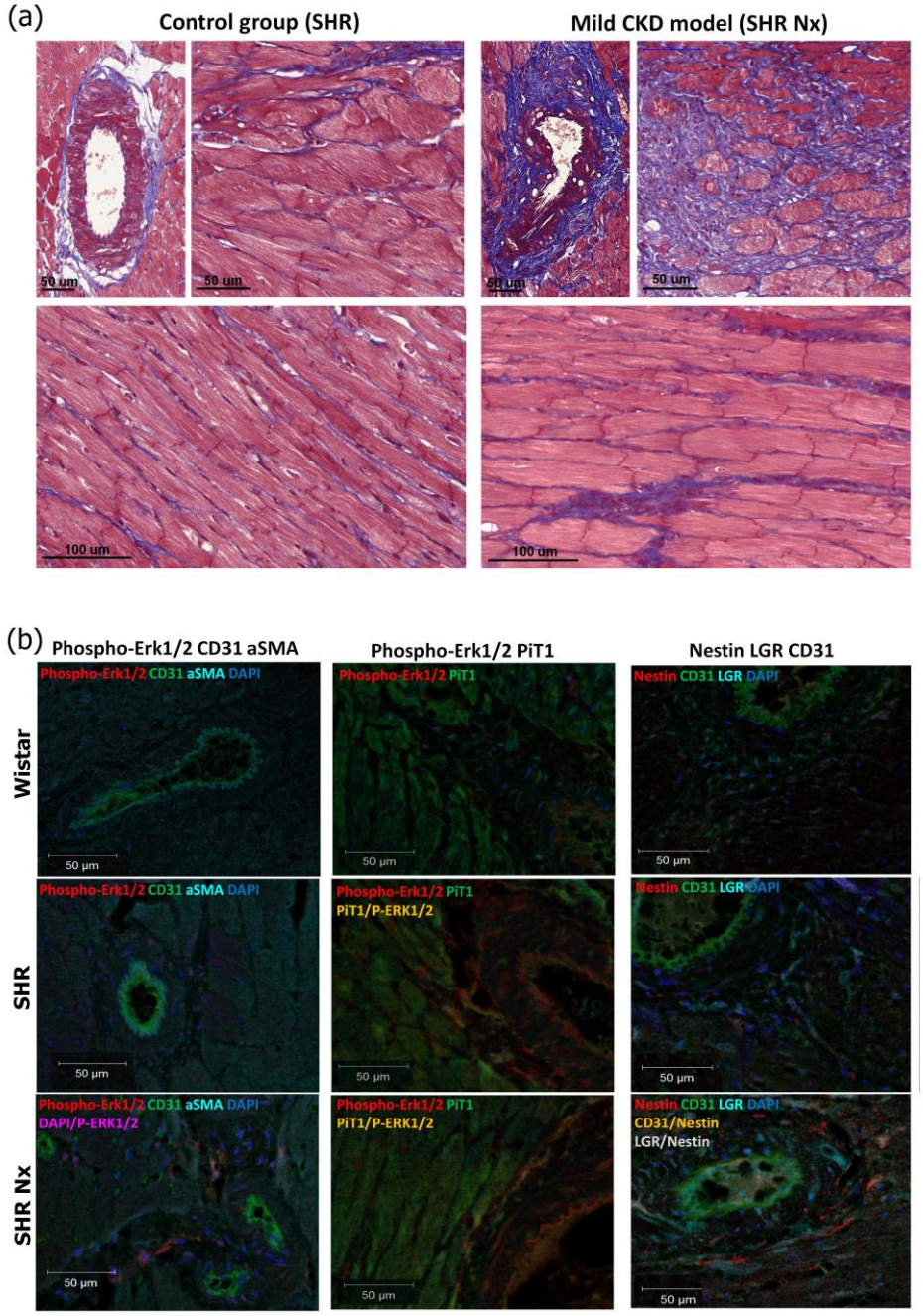

Figure 1 – Myocardial remodeling in mild CKD model vs. control:
(a) Masson's staining, (b) signaling molecules co-expression