University of Antwerp

Impaired vascular function contributes to exercise intolerance in chronic kidney disease

Antwerp University Hospital

A.H.Van Craenenbroeck[1,2,4], E. M.Van Craenenbroeck[1,3], K.Van Ackeren[1], V.Y. Hoymans[1], G.A.Verpooten[4], C. J.Vrints[1,3], M. M. Couttenye[2]

(1) Laboratory of Cellular and Molecular Cardiology, University of Antwerp; (2) Department of Nephrology & (3) Department of Cardiology, Antwerp University Hospital; (4) Laboratory of Experimental Medicine and Pediatrics, University of Antwerp

INTRODUCTION AND OBJECTIVES

- Exercise intolerance is an important feature in patients with CKD and is prognostic for both increased morbidity and mortality, but underlying mechanisms are still unknown
- The aim of this study is to gain more insight into the clinical, cellular and molecular determinants of exercise capacity in predialysis CKD

METHODS

CLINICAL

- CKD stage 1-5 without cardiovascular disease
- Healthy subjects

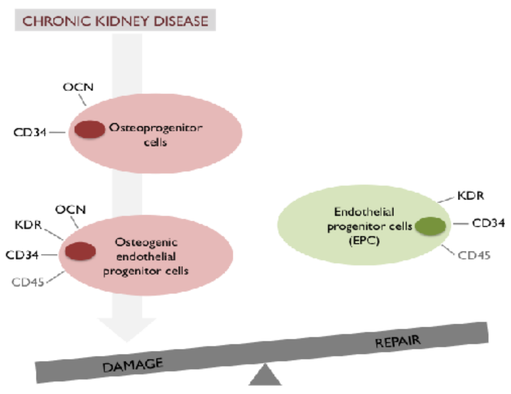
Echocardiography
ECG
Cardiopulmonary exercise test
Flow-mediated dilation
Carotid-femoral pulse wave velocity

Peak aerobic capacity and vascular function

	Bivariate correlation		Multiple regression	
	Pearson r	p-value	ß	p-value
Age	-0.285	0.011	-0.172	0.168
eGFR	0.525	<0.001	0.363	0.002
Hemoglobin	0.372	0.001	0.199	0.089
FMD	0.360	0.003	0.162	0.169
PWV	-0.435	<0.001	-0.301	0.010

CELLULAR

Progenitor cells: imbalance between damage and repair



MOLECULAR

microRNA: short, endogenous, non-coding RNAs that negatively regulate gene expression at the posttranscriptional level

Studied microRNA

microRNA	Biological process	Validated target genes
miR-21	Inflammation, Apoptosis, Hypoxia/ischemia adaptation	PTEN, PDC4, BCL-2
miR-126	Angiogenesis	Spred-1, PI3KR2, SDF-1
miR-146a	Inflammation	IRAK-1, TRAF6, CXCR4, TLR4
miR-150	Hematopoiesis, progenitor cell mobilisation and migration	CXCR4, MYB, FLT3, CBL, EGR2, AKT2 and DKC
miR-210	Angiogenesis, hypoxia, proliferation	HIF-1a

RESULTS

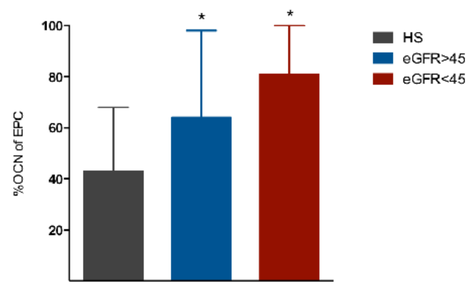
Aerobic capacity and vascular function in relation to eGFR

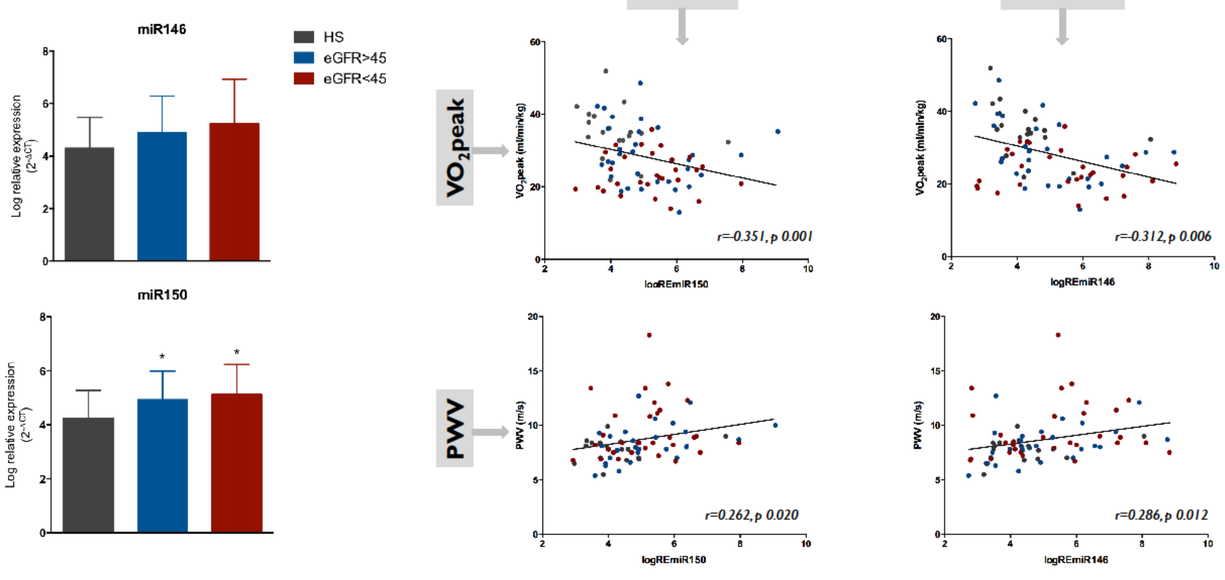
	HS (n=18)	**eGFR>45** (n=32)	**eGFR<45** (n=31)	*p-value*
Age (years)	54.9 ± 3.3	47.1 ± 13.9	53.4 ± 14.6	0.061
Sex (F/M)	8/10	16/16	15/16	0.931
SBP (mmHg)	125 ± 19	125 ± 16	126 ± 16	0.940
DBP (mmHg)	80 ± 11	83 ± 13	80 ± 10	0.559
Framingham risk (%)	4.1 ± 3.4	3.5 ± 4.7	5.9 ± 7.4	0.256
Estimated GFR (CKD-EPI)	87.9 ± 8.5	63.6 ± 17.6*	24.8 ± 8.9*	<0.001
Hemoglobin (g/dl)	14.02 ± 1.13	13.87 ± 1.29	12.78 ± 1.19*	<0.001
VO_2 peak (ml/kg/min)	35.99 ± 6.43	28.13 ± 8.34*	24.05 ± 5.44*	<0.001
%predicted VO_2 peak	125 ± 22	88 ± 23*	83 ± 21*	<0.001
VO_2 at AT (ml/kg/min)	30.83 ± 7.33	25.08 ± 7.47*	21.31 ± 3.53*	<0.001
Maximal workload (Watt)	205 ± 60	171 ± 55	141 ± 47*	0.001
Exercise duration (sec)	536 ± 186	430 ± 126*	390 ± 105*	0.004
RER	1.40 ± 0.09	1.36 ± 0.13	1.36 ± 0.11	0.455
FMD (%)	6.93 ± 3.46	5.86 ± 3.21	4.93 ± 2.51*	0.025
PWV (m/s)	7.78 ± 1.03	8.35 ± 1.66	9.50 ± 2.66*	0.012

EPC and OPC in relation to eGFR

	HS (n=18)	**eGFR>45** (n=32)	**eGFR<45** (n=31)	*p-value*
EPC/10^6 events	19.25 ± 16.39	34.96 ± 41.49	38.67 ± 38.82	0.155
OPC/10^6 events	127 ± 97	180 ± 155	255 ± 274	0.146

Osteogenic progenitor cells





CONCLUSION

- Arterial stiffness contributes independently to the observed exercise intolerance in predialysis CKD
- Progenitor cells with osteogenic capacity, as well as circulating miR-146a and miR-150, may play a role in the pathophysiology of arterial stiffness in this population

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