Structural abnormalities of the heart and vascular system in CKD & Dialysis

- Thick but weak

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Cardiovascular pathology in CKD

LVH

atherosclerosis

calcification

fibrosis

microarteriopathy

reduction in capillarisation

arteriosclerosis
Cardiovascular pathology in CKD - crosstalk between kidney and cardiovascular system

- LVH
- cardiac fibrosis
- impaired angioadaptation with reduced ischemia tolerance (role of VEGF and the sympathetic nervous system)
- accelerated arterio- and atherosclerosis (calcification and inflammation)
Cardiovascular pathology in CKD - crosstalk between kidney and cardiovascular system

- LVH: is very common and develops early on in CKD
- cardiac fibrosis
- impaired angioadaptation with reduced ischemia tolerance (role of VEGF and the sympathetic nervous system)
- accelerated arterio- and atherosclerosis (calcification and (micro-) inflammation)
Prevalence of LV disorders in CKD

84% of patients starting dialysis already show LV alterations

(Parfrey et al, NDT 1996)
„Uremic cardiomyopathy“ / cardiomyopathy in advanced CKD
Relative heart weight and left ventricular weight

(Amann et al, JASN 1998)
Morphology of the myocardium in experimental CKD

→ LVH already present after 3 weeks (20 - 60% increase in LV weight)
→ LV contractility: - 40%
→ prevented and reversed (!) by ACE-i and mTOR inhibition
LVH in SNX is accompanied by increased apoptosis and loss of cardiomyocytes

SNX  
sham

Nakamura et al. 2010:  
↑cyclin D2, ↑PCNA, ↓CDK-inhibitor p27 (as novel markers of LVH)

→ myocyte loss (-25%) in CKD predisposes to cardiac failure!
→ experimentally prevented by ACE-i and mTOR inhibition!
Cardiovascular pathology in CKD - crosstalk between kidney and cardiovascular system

- LVH
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Increased volume density of the myocardial interstitial tissue in CKD

→ early and specific activation of myocardial interstitial cells in CKD

→ pathogenetic role of PTH, P, AngII and ET-1 (via TGF-β)
Functional consequences of cardiac fibrosis

- reduced LV compliance
- altered stress – strain relationship
- arrhythmia
  - interposition of fibrous tissue with high electrical resistance
  - local delay in spread of action potential
  - reentry type of arrhythmia

→ sudden cardiac death
Cardiovascular pathology in CKD - crosstalk between kidney and cardiovascular system

- LVH
  → FGF23, a new kid on the block?
- cardiac fibrosis

- impaired angioadaptation with reduced ischemia tolerance
  (role of VEGF and the sympathetic nervous system)

- accelerated arterio- and atherosclerosis
  (calcification and inflammation)
Fibroblast Growth Factor 23 and Left Ventricular Hypertrophy in Chronic Kidney Disease
Orlando M. Gutiérrez, James L. Januzzi, Tamara Isakova, Karen Laliberte, Kelsey Smith, Gina Collerone, Ammar Sarwar, Udo Hoffmann, Erin Cogliani, Robert Christenson, Thomas J. Wang, Christopher deFilippi and Myles Wolf

Figure 1. Mean concentrations of log FGF-23 and phosphate according to level of kidney function. Bars represent SDs; shaded areas, normal ranges for each analyte.

Figure 2. Correlation between log FGF-23 and LVMI ($r=0.27$, $P<0.001$). □ Indicates non-CKD subjects; ■, subjects with CKD.
FGF23 induces left ventricular hypertrophy

Christian Faul,1,2 Ansel P. Amaral,1,2 Behzad Oskouei,3 Ming-Chang Hu,4,5,6 Alexis Sloan,1,2 Tamara Isakov,1 Orlando M. Gutiérrez,7 Robier Aguillon-Prada,1 Joy Lincoln,8 Joshua M. Hare,3 Peter Mundel,9 Azorides Morales,10 Julia Scialla,1 Michael Fischer,11,12 Elsayed Z. Soliman,13 Jing Chen,14 Alan S. Go,15 Sylvia E. Rosas,16 Lisa Nessel,17 Raymond R. Townsend,16 Harold I. Feldman,16,17 Martin St. John Sutton,18 Akinlolu Ojo,19 Crystal Gadegbeku,20 Giovana Seno Di Marco,21 Stefan Reuter,21 Dominik Kentrup,21 Klaus Tiemann,22 Marcus Brand,21 Joseph A. Hill,4,23 Orson W. Moe,4,6,24 Makoto Kuro-o,6,25 John W. Kusek,26 Martin G. Keane,18 and Myles Wolf1

A

Heart weight/ tibial length (mg/mm)

Untreated Vehicle FGF23

8.5

8

7.5

7

6.5

Untreated Vehicle FGF23

B

LV wall thickness (mm)

Untreated Vehicle FGF23

2.5

2

1.5

1

0.5

Untreated Vehicle FGF23

Left ventricular free wall Interventricular septum

C

Untreated Vehicle FGF23

MC

7 d 14 d 7 d 14 d

D

Myocyte cross-sectional area (sqμm)

Untreated Vehicle FGF23

E

Ejection fraction (%)

Day 0 Day 7 Day 14

(JCI 2011)
Klotho and Phosphate Are Modulators of Pathologic Uremic Cardiac Remodeling


→ synergy of high-phosphate diet, Klotho deficiency and aging on cardiac remodelling

(JASN 2015)
Physiologic processes

- Vitamin D
- PTH

Pathologic processes

- FGF23
- Vascular dysfunction and atherosclerosis
- Secondary hyperparathyroidism
- Left ventricular hypertrophy
+ cardiac fibrosis

- Normal conditions
- Altered conditions

J. Donate-Correa et al./Cytokine & Growth Factor Reviews 23 (2012) 37-46
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- LVH
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- impaired angioadaptation with reduced ischemia tolerance (role of VEGF and the sympathetic nervous system)
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Decrease of myocardial capillarisation in CKD

*\( \text{p} < 0.05 \text{ vs uremia} \)

(Amann et al. JASN 1998)
Myocyte-capillary mismatch in experimental CKD

- 25% reduction of capillary supply
  (can be prevented by blockade of the sympathetic nervous system and the ET system !)
Capillary rarefaction in SNX leads to increased myocardial damage after coronary artery ligation

Area of infarction (in % LV) :
- 18.8 ± 6.6 % in sham
- 30.6 ± 6.7 % in SNX
  (p<0.05)

→ reduced myocardial ischemia tolerance in SNX!
Vascular maladaptation in CKD under ischemic conditions

Lack of adaptive VEGF-regulation in CKD under ischemic conditions (LVH and hind-limb)

![Diagram showing VEGF mRNA and protein levels in sham and SNX conditions.](image)

**VEGF mRNA**
- Sham: Blue bar
- SNX: Red bar

**VEGF-protein**
- Sham: Blue bar
- SNX: Red bar

*Significant difference (*) compared to sham.
The Soluble VEGF Receptor sFlt1 Contributes to Endothelial Dysfunction in CKD

Giovana S. Di Marco,* Stefan Reuter,* Uta Hillebrand,**† Susanne Amler,† Maximilian König,* Etienne Larger,§ Hans Oberleithner,† Eva Brand,* Hermann Pavenstädt,* and Marcus Brand*

A

<table>
<thead>
<tr>
<th>Serum sFlt-1 (pg/ml)</th>
<th>Sham</th>
<th>5/6 Nx</th>
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B

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<th>Serum sVCAM (ng/ml)</th>
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A

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<tr>
<th>sFlt-1 RNA levels (normalized to GAPDH)</th>
<th>Controls</th>
<th>Patients</th>
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<tr>
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<tr>
<th>sFlt-1 protein levels (pg/mg cell protein)</th>
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→ anti-angiogenic effect of CKD serum with ↑apoptosis of EC and ↓NO
Soluble Flt-1 links microvascular disease with heart failure in CKD

Giovana S. Di Marco¹ · Dominik Kentrup¹ · Stefan Reuter¹ · Anna B. Mayer¹ · Lina Golle¹ · Klaus Tiemann² · Manfred Fobker³ · Christiane Engelbertz⁴ · Günter Breithardt⁴ · Eva Brand¹ · Holger Reinecke³ · Hermann Pavenstädt¹ · Marcus Brand¹
Elevated sFLT-1 levels reduce capillary density in the heart
Cardiovascular pathology in CKD - crosstalk between kidney and cardiovascular system

- LVH
- cardiac fibrosis
- impaired angioadaptation with reduced ischemia tolerance (role of VEGF and the sympathetic nervous system)
- accelerated arterio- and atherosclerosis (calcification and (micro-) inflammation)
Accelerated arteriosclerosis in CKD - Uremic arteriopathy

fibrous or fibro-elastic intimal thickening

Epigastric artery of a 46y old patient at the time of renal transplantation
Wall thickening of coronary arteries in CKD

(Schwarz et al., NDT 2000)
Arterial wall thickening in CKD is accompanied by ultrastructural changes.

- Normal morphology of aortic media (sham)
- Media thickening with hyperplasia of VSMC, increased ECM and reduced elastic fibre content

→ reduced vascular elasticity, increased vascular wall stiffness, RR ↑, LVH ↑, calcification ↑
Atherosclerosis in CKD?

more common?

more severe?

specific characteristics?
Atherosclerosis in CKD

<table>
<thead>
<tr>
<th>Type</th>
<th>No Renal Disease (n=27)</th>
<th>Renal Disease (n=27)</th>
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<tr>
<td>VIII</td>
<td>0</td>
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X-ray diffraction analysis of coronary plaques

→ pro-inflammatory phenotype of atherosclerotic plaques in CKD!
Cardiovascular pathology in CKD

- LVH
- fibrosis
- reduction in capillarisation
- microarteriopathy
- atherosclerosis
- arteiosclerosis
- calcification
Phenotypic alterations in uremia

Intradialytic hypotension

(Smith et al. 2009)
Heart and Kidney: Fatal Twins?

Eberhard Ritz, MD
Department of Nephrology, Ruprecht-Karl University, Heidelberg, Germany

The pathologic mechanisms that underlie the progression of cardiovascular and renal damage are common to both, and this, coupled with evidence that renal damage can precipitate cardiovascular damage, reinforces the importance of targeting early renal disease with appropriate therapy in order to reduce the prevalence of cardiovascular disease. As has been succinctly summarized by de Zeeuw et al, we should “treat the kidney to protect the heart.”61
Thank you very much!