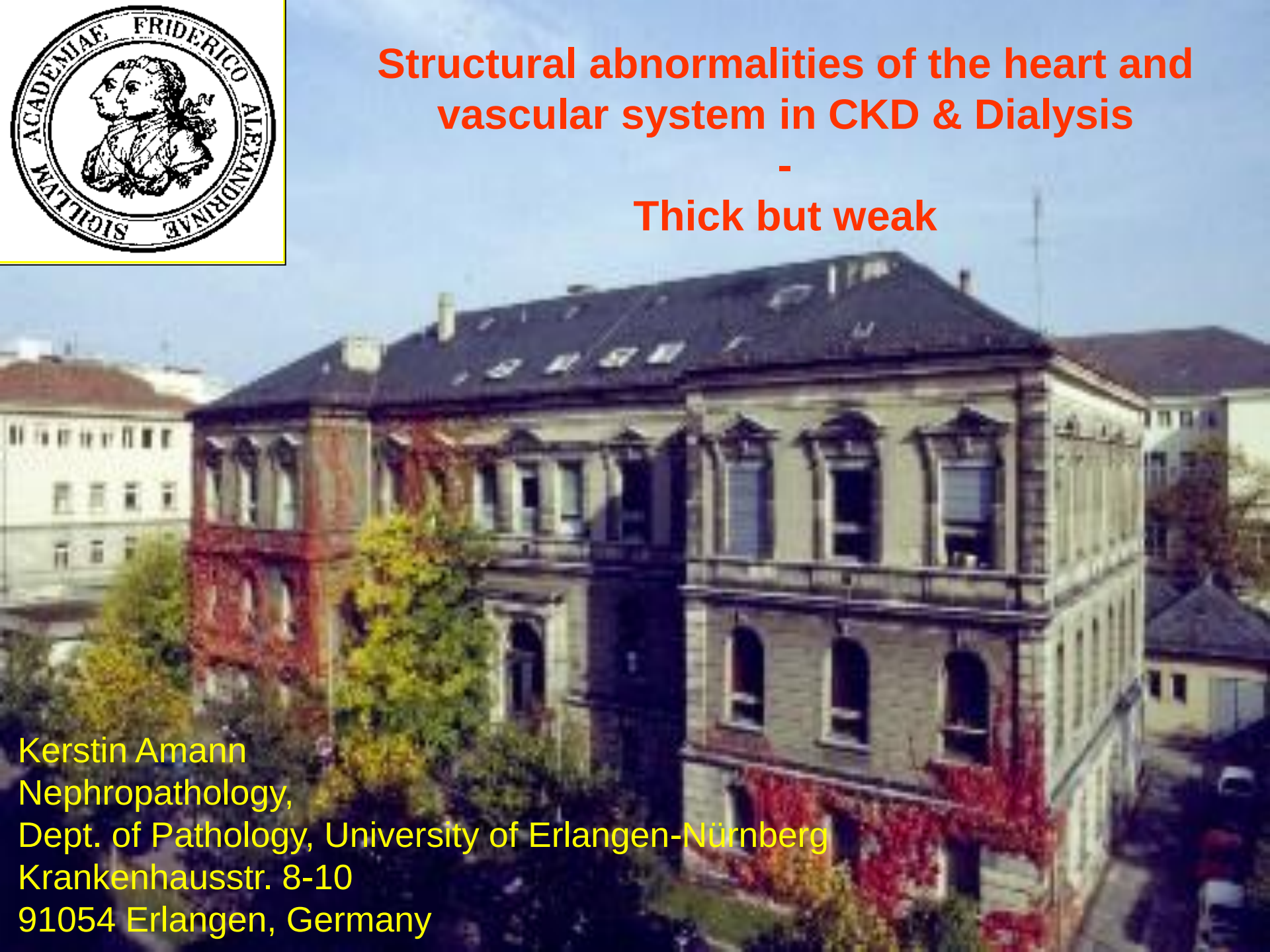
Structural abnormalities of the heart and vascular system in CKD & Dialysis

-

Thick but weak



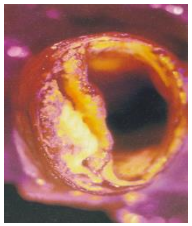
Kerstin Amann
Nephropathology,
Dept. of Pathology, University of Erlangen-Nürnberg
Krankenhausstr. 8-10
91054 Erlangen, Germany

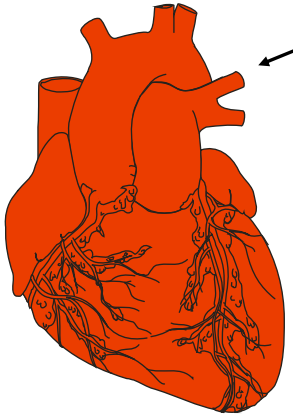
Cardiovascular pathology in CKD

LVH

atherosclerosis

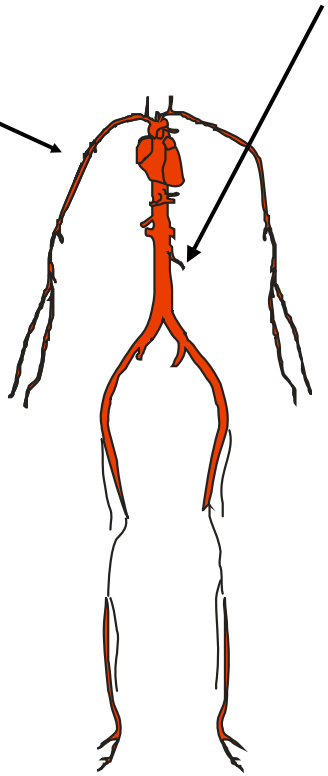
calcification

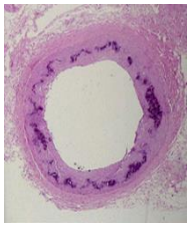




fibrosis

microarteriopathy





reduction in capillarisation

arteriosclerosis

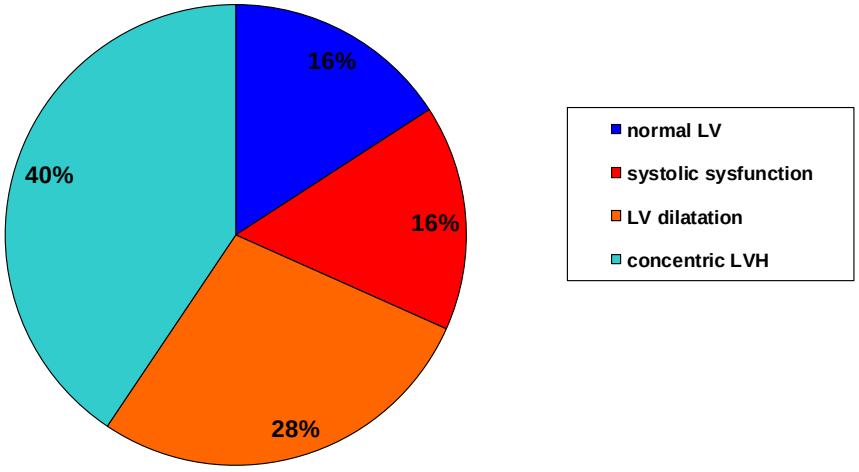
Cardiovascular pathology in CKD - crosstalk between kidney and cardiovascular system

- LVH
- cardiac fibrosis
- impaired angioadaptation with reduced ischemia tolerance
  (role of VEGF and the sympathetic nervous system)
- accelerated arterio- and atherosclerosis
  (calcification and inflammation)

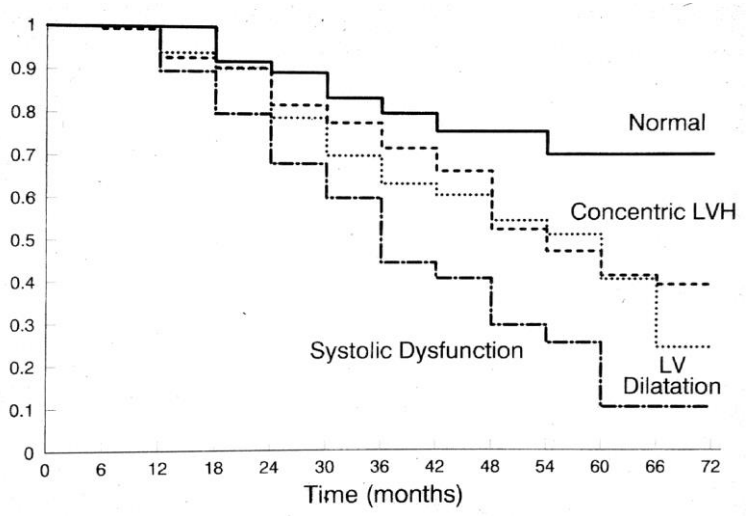
Cardiovascular pathology in CKD - crosstalk between kidney and cardiovascular system

- **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



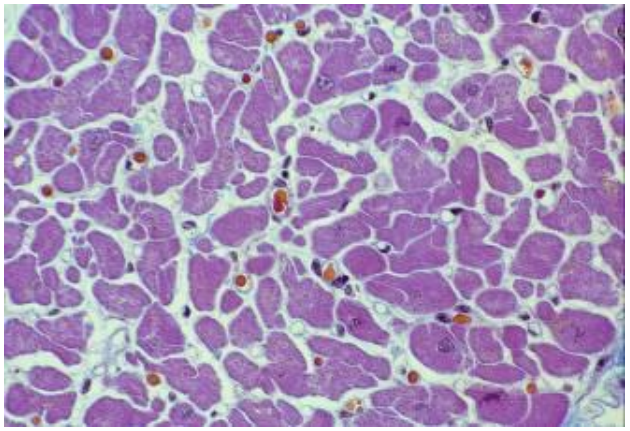
84% of patients starting dialysis already show LV alterations



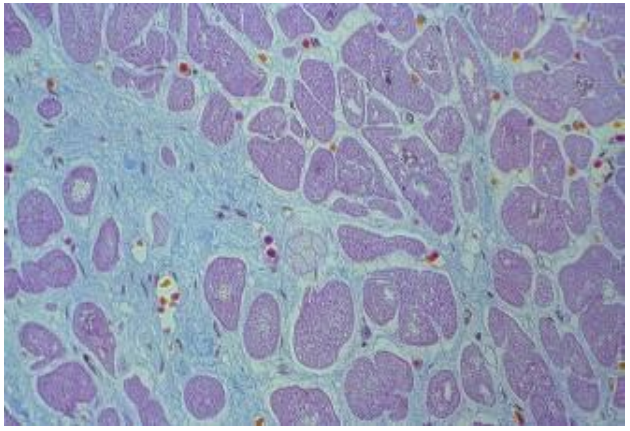
time until development of end-stage heart failure

(Parfrey et al, NDT 1996)

„Uremic cardiomyopathy“ / cardiomyopathy in advanced CKD

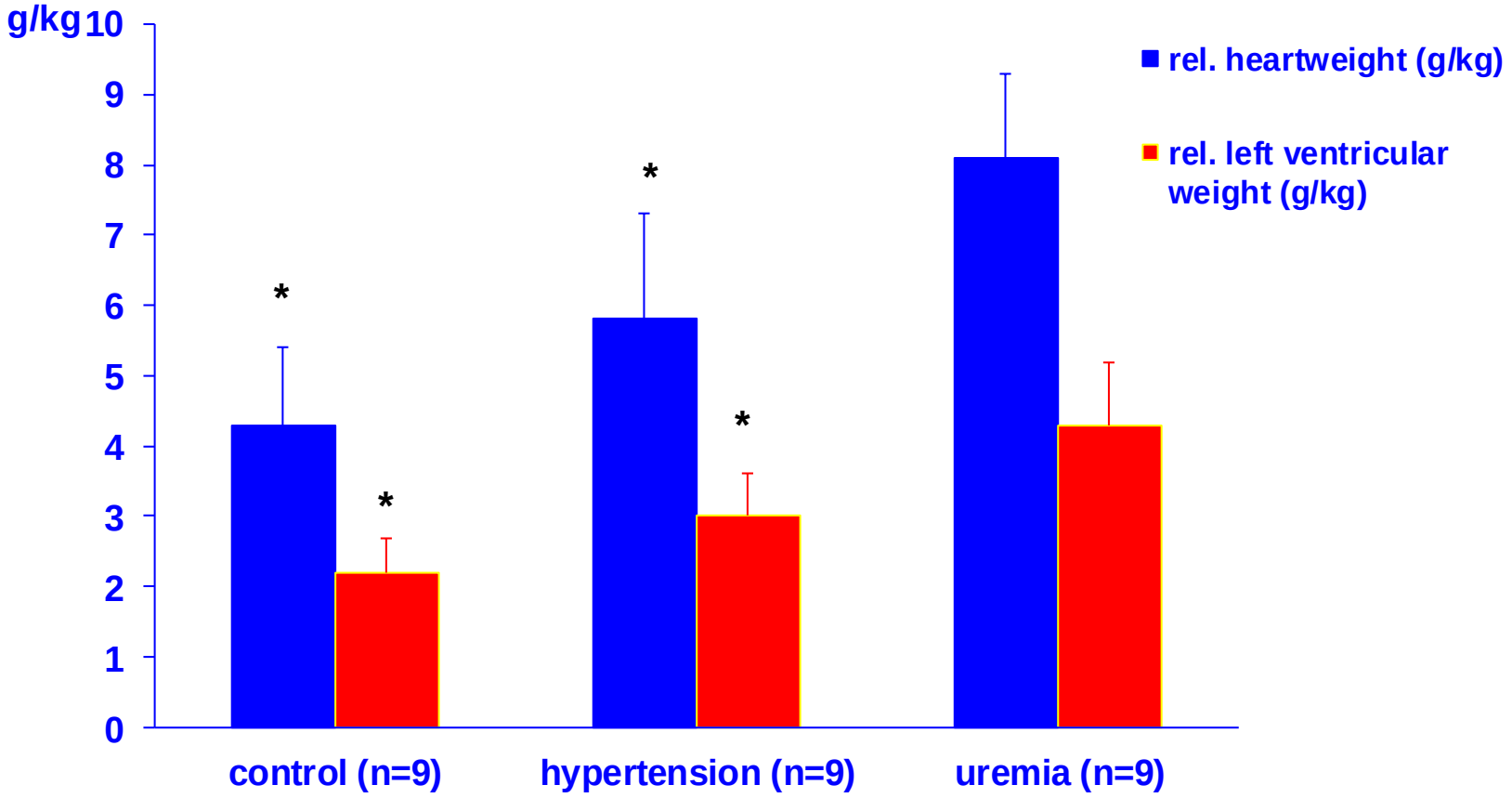


control



CKD

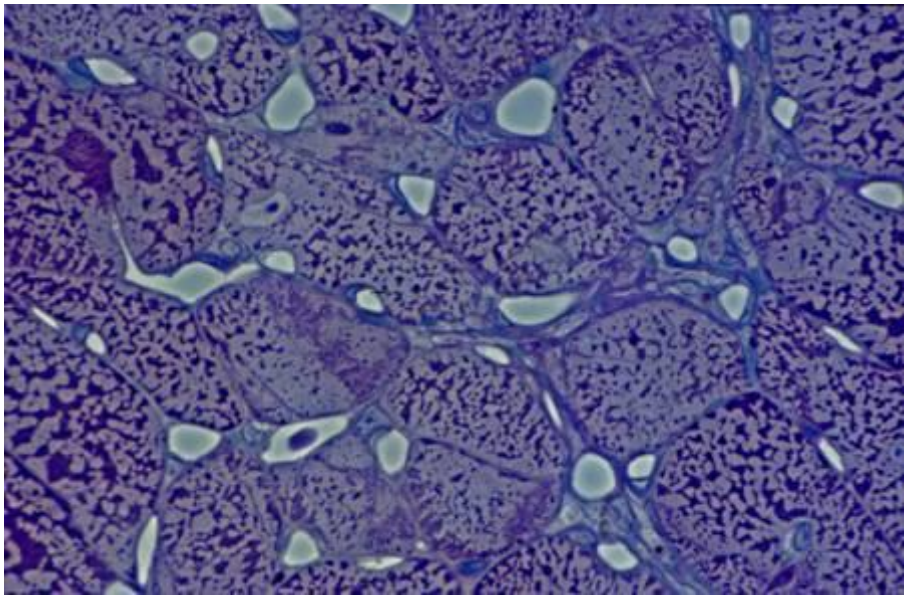
Relative heart weight and left ventricular weight



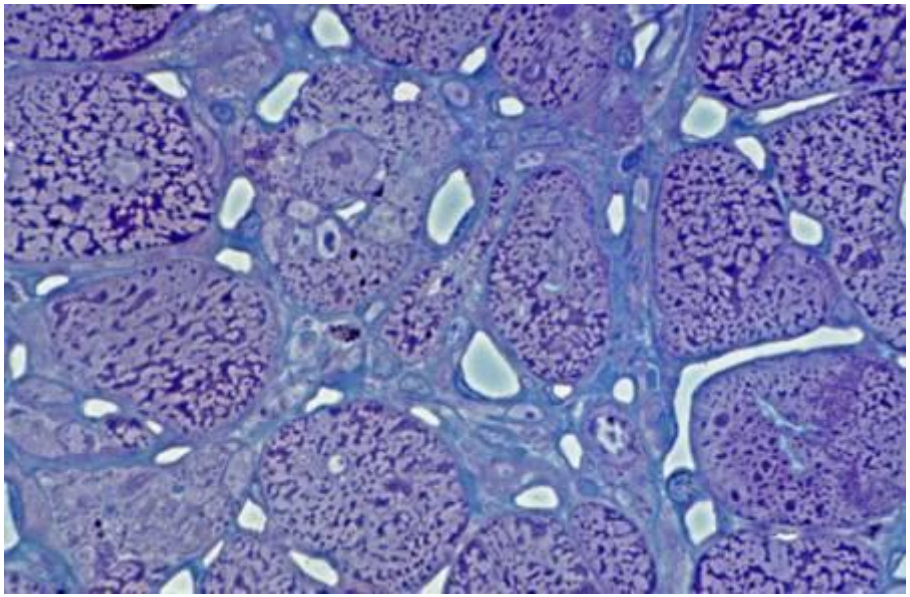
(Amann et al, JASN 1998)

(*:p<0.05 vs uremia)

Morphology of the myocardium in experimental CKD



sham

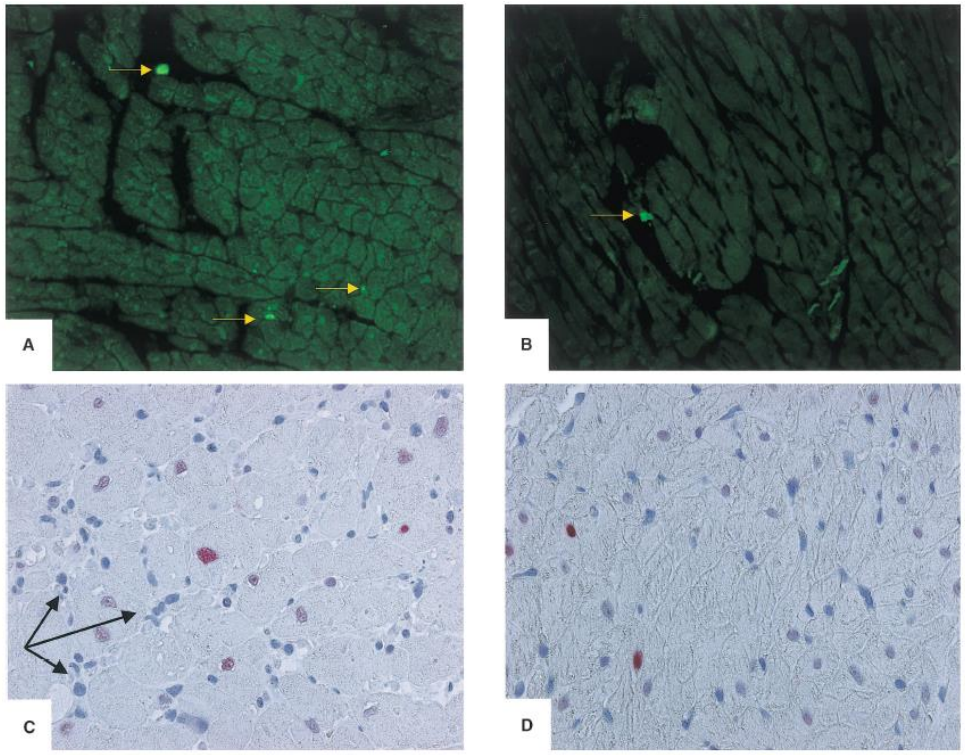


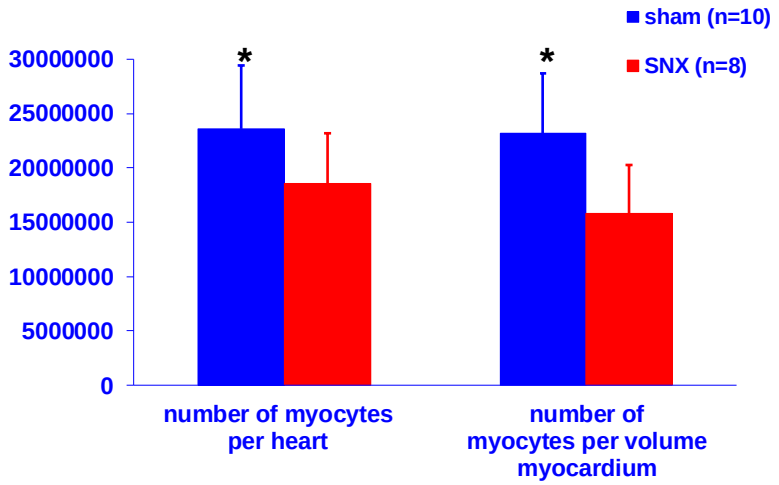
SNX

→ 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





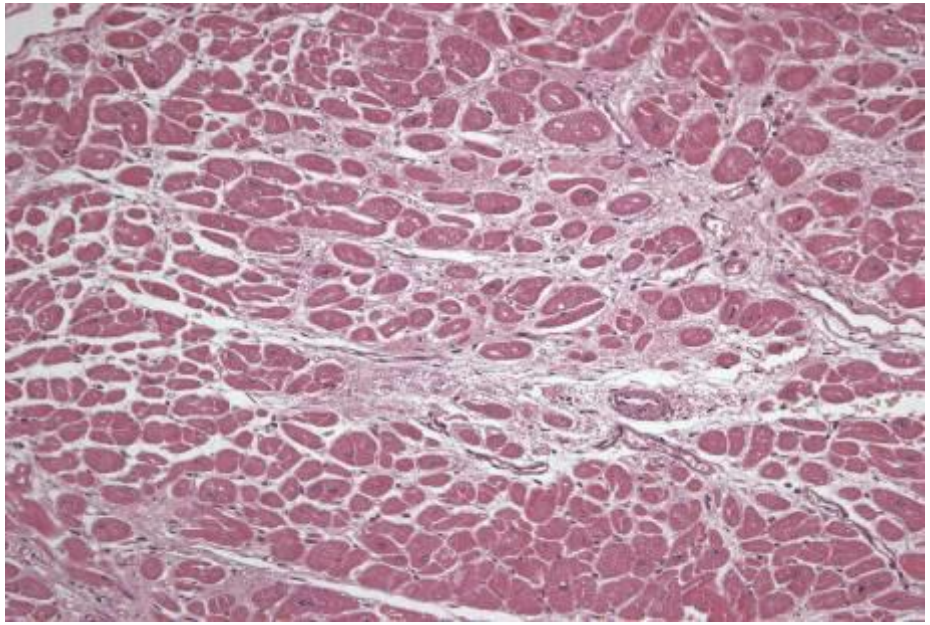
Nakamura et al. 2010:
↑cyclin D2, ↑PCNA, ↓CDK-inhibitor p27 (as novel markers of LVH)

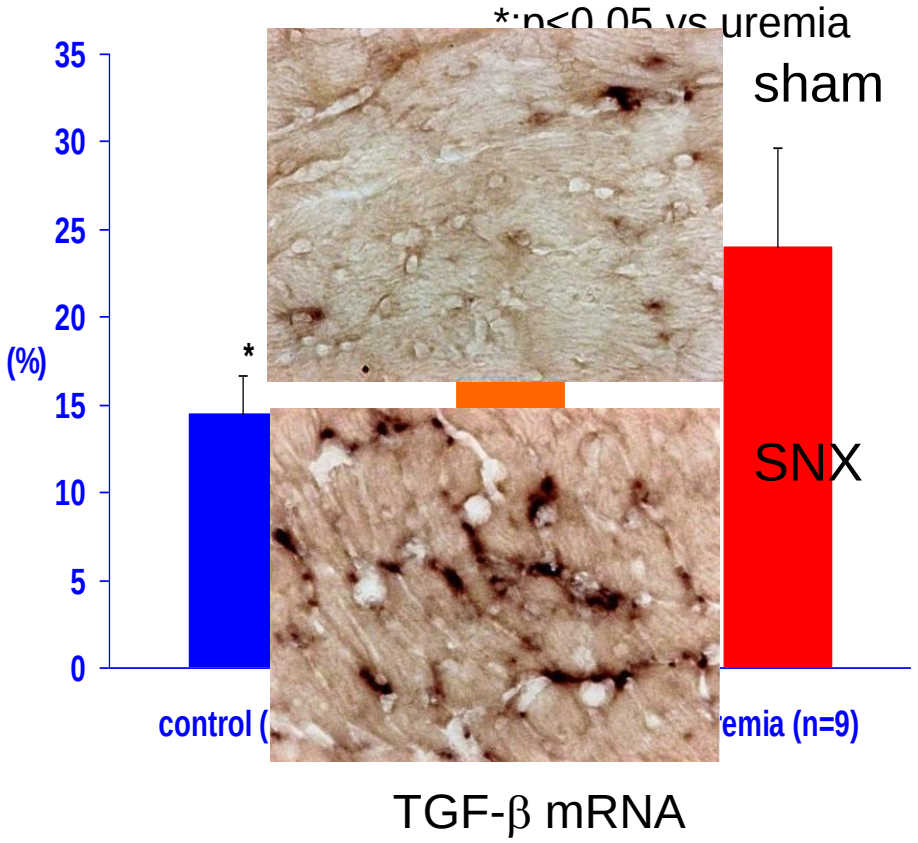
→ myocyte loss (-25%) in CKD predisposes to cardiac failure !
→ experimentally prevented by ACE-i and mTOR inhibition!

Cardiovascular pathology in CKD - crosstalk between kidney and cardiovascular system

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

Increased volume density of the myocardial interstitial tissue in CKD





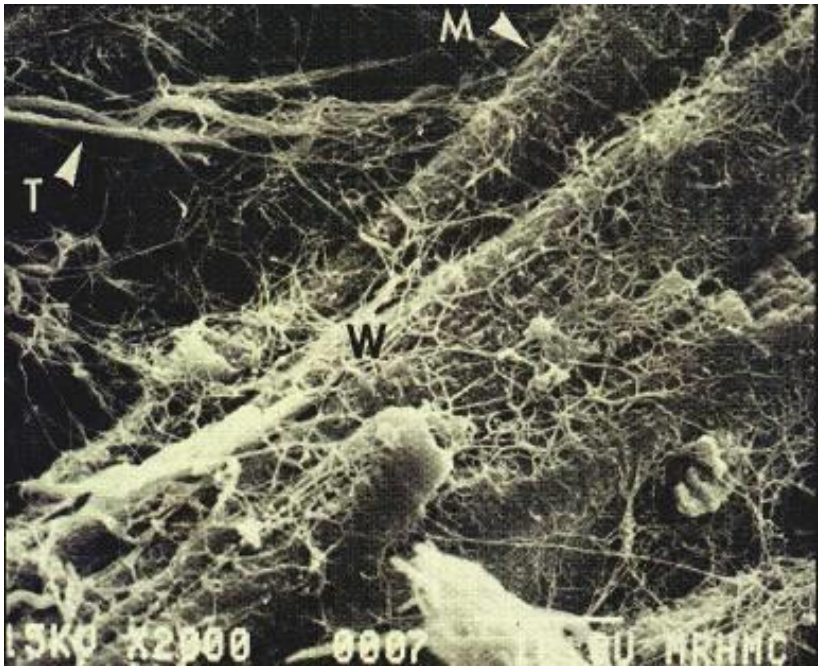
TGF-β mRNA

→ early and specific activation of myocardial interstitial cells in CKD

→ pathogenetic role of PTH, P, AngII and ET-1 (via TGF-ß)

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)

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association®
Learn and Live℠

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 Coglianese, Robert Christenson, Thomas J. Wang, Christopher deFilippi and Myles Wolf

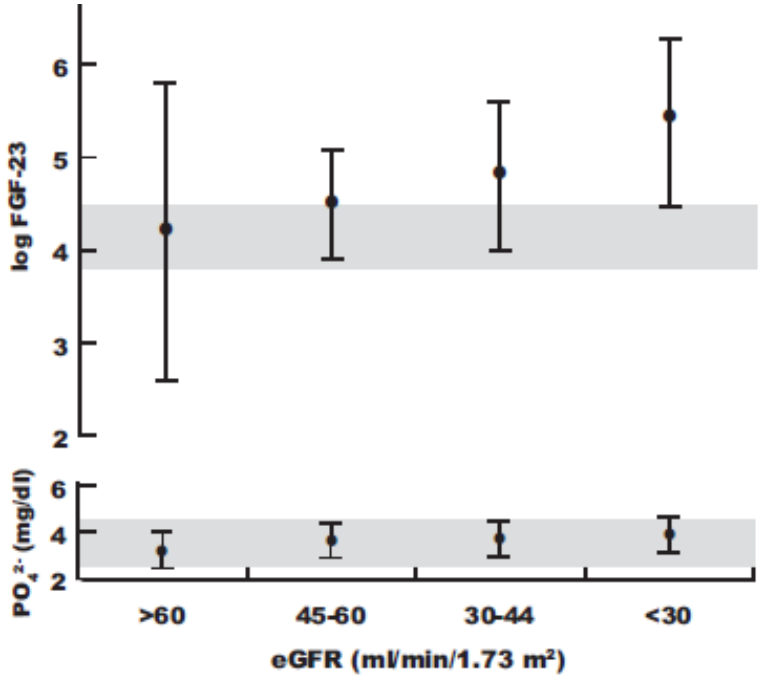


Figure 1. Mean concentrations of log FGF-23 and phosphate according to level of kidney function. Bars represent SDs; shaded areas, normal ranges for each analyte.

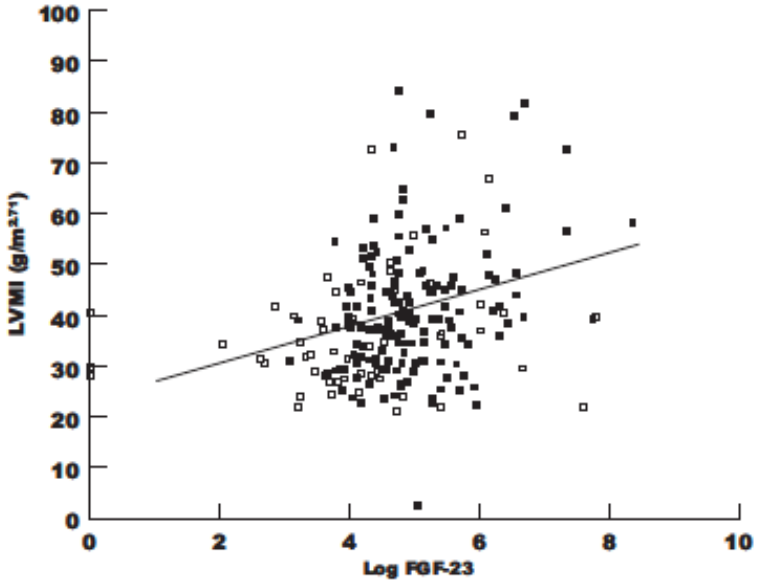
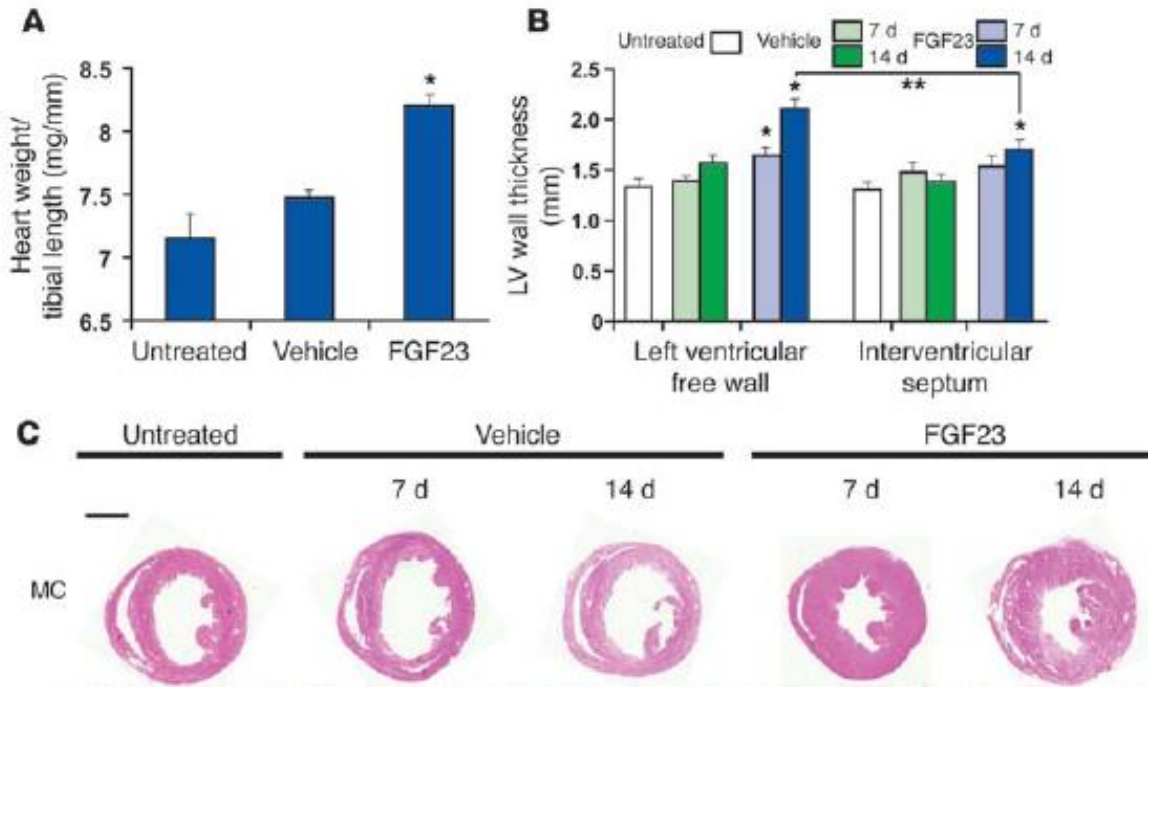


Figure 2. Correlation between log FGF-23 and LVMI (r=0.27, P<0.001). □ Indicates non-CKD subjects; ■, subjects with CKD.

FGF23 induces left ventricular hypertrophy

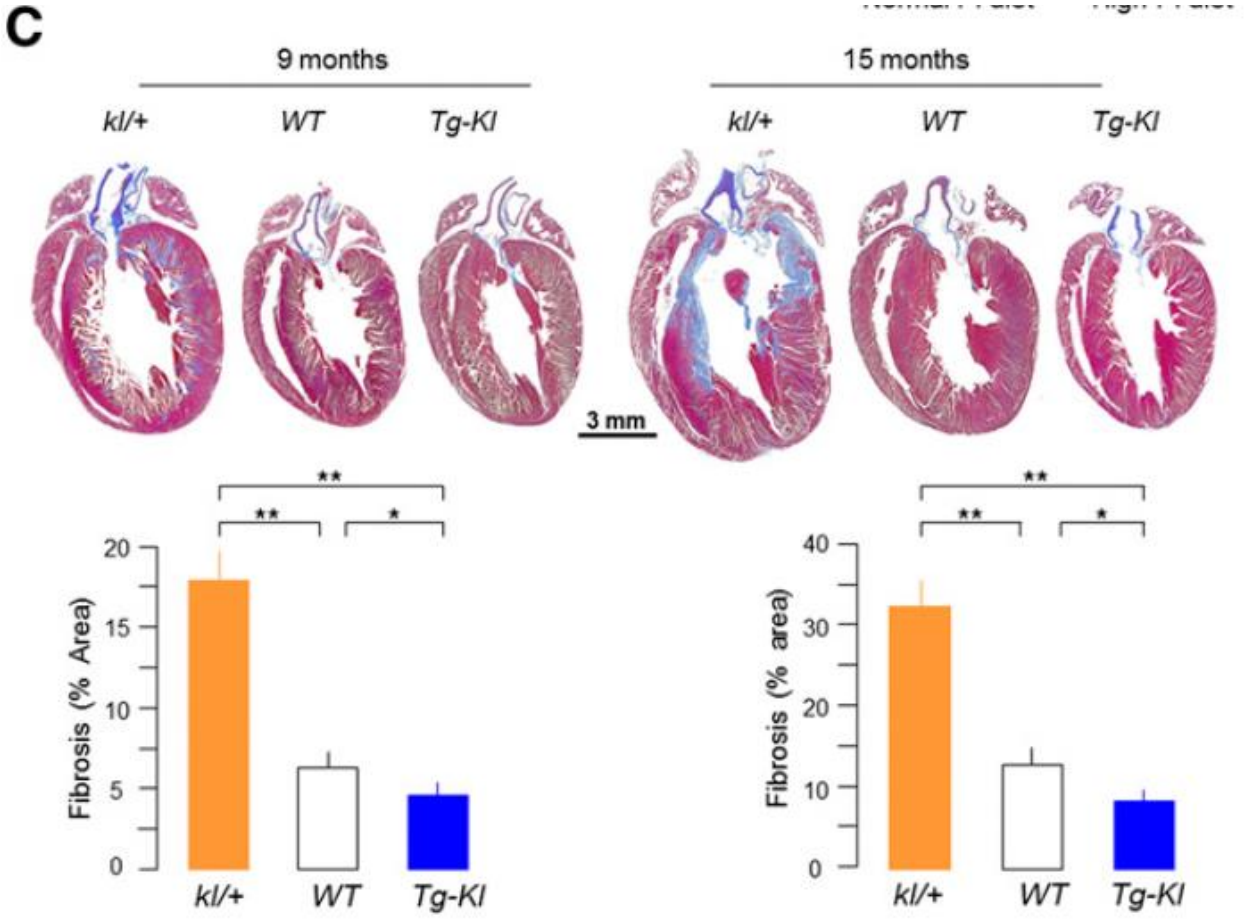
Christian Faul,[1,2] Ansel P. Amaral,[1,2] Behzad Oskouei,[3] Ming-Chang Hu,[4,5,6] Alexis Sloan,[1,2] Tamara Isakova,[1] Orlando M. Gutiérrez,[7] Robier Aguillon-Prada,[1] Joy Lincoln,[8] Joshua M. Hare,[3] Peter Mundel,[9] Azorides Morales,[10] Julia Scialla,[1] Michael Fischer,[11,12] Elsayed Z. Soliman,[13] 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 Wolf[1]



(JCI 2011)

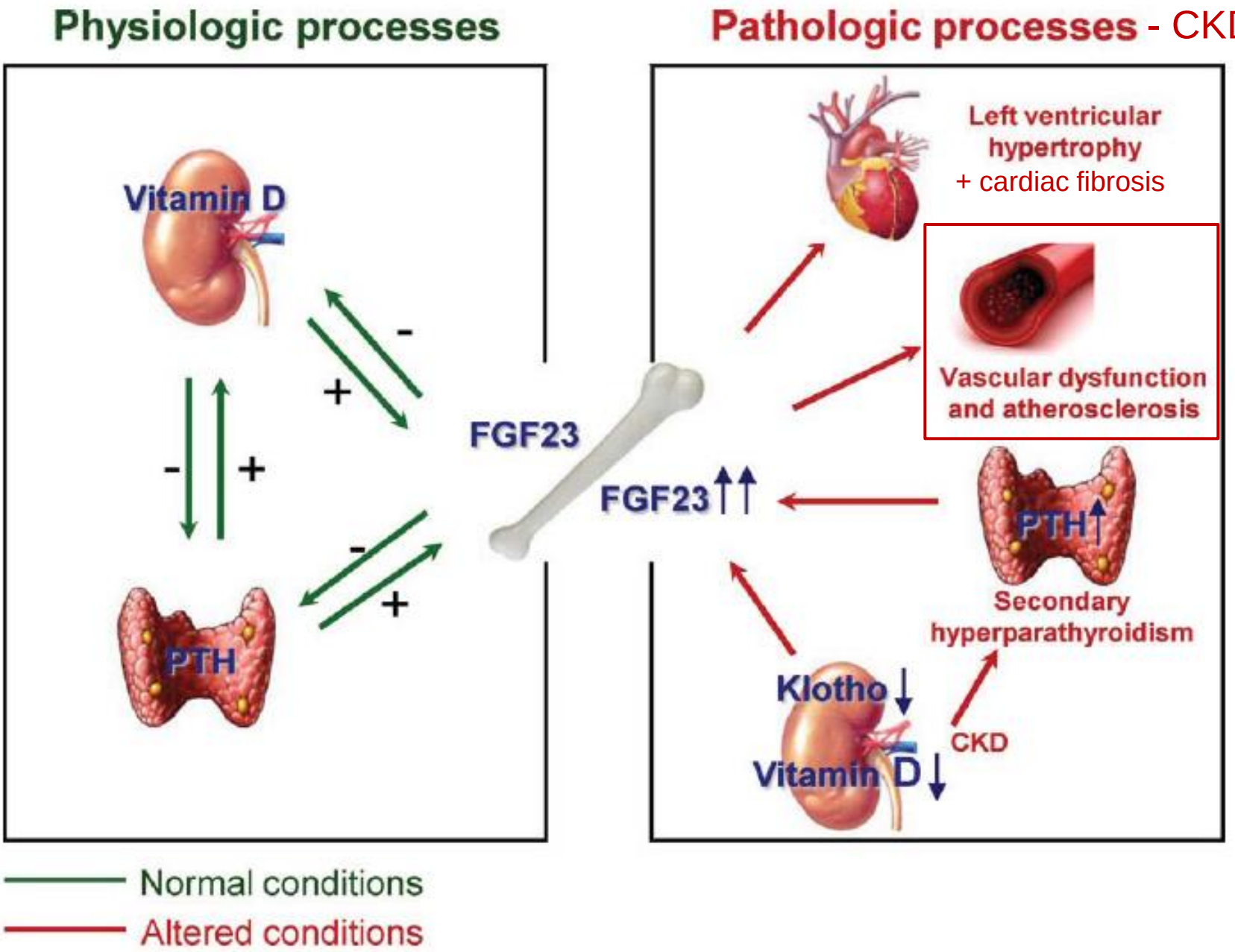
Klotho and Phosphate Are Modulators of Pathologic Uremic Cardiac Remodeling

Ming Chang Hu,*† Mingjun Shi,* Han Jun Cho,* Beverley Adams-Huet,*†‡ Jean Paek,* Kathy Hill,* John Shelton,§ Ansel P. Amaral,‖¶ Christian Faul,‖¶ Masatomo Taniguchi,*‡ Myles Wolf,‖ Markus Brand,** Masaya Takahashi,†† Makoto Kuro-o,*§ Joseph A. Hill,†‡‡ and Orson W. Moe*†§§



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

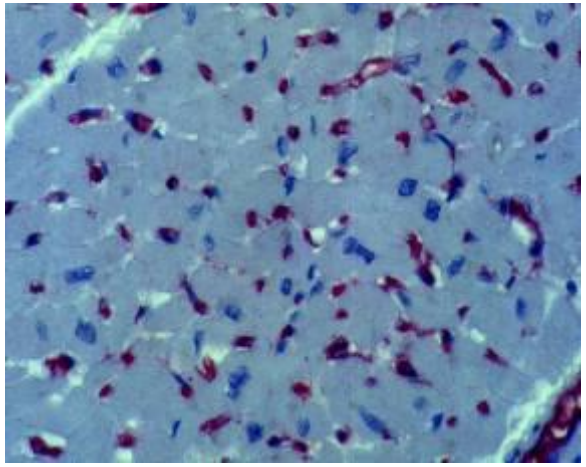
(JASN 2015)


Physiologic processes
Pathologic processes - CKD
Vitamin D
FGF23
PTH
Left ventricular hypertrophy
+ cardiac fibrosis
Vascular dysfunction and atherosclerosis
FGF23
PTH
Secondary hyperparathyroidism
Klotho
Vitamin D
CKD
Normal conditions
Altered conditions

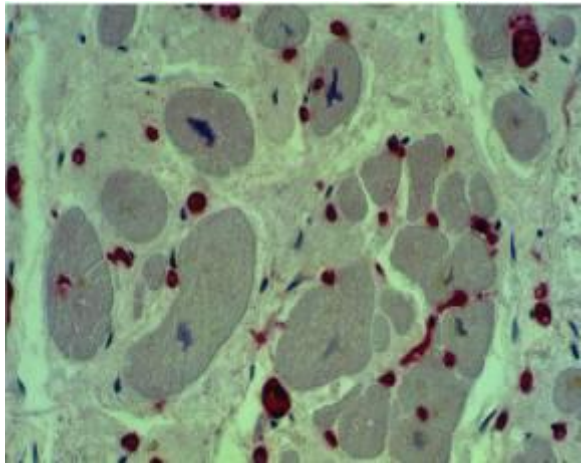
Cardiovascular pathology in CKD - crosstalk between kidney and cardiovascular system

- 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)

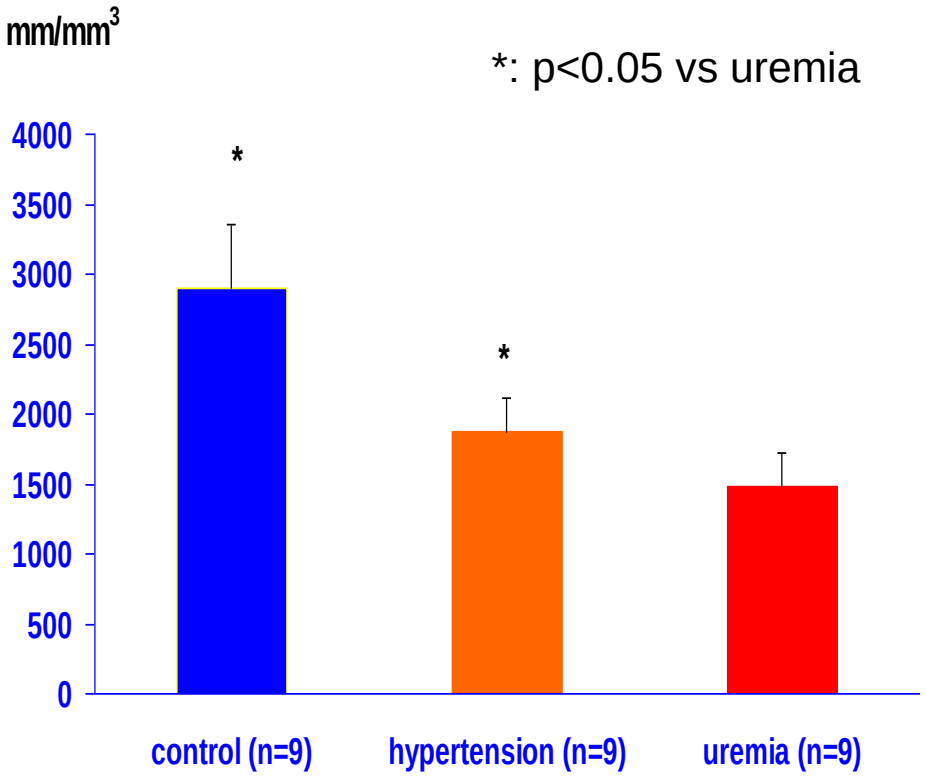
Decrease of myocardial capillarisation in CKD



control patient

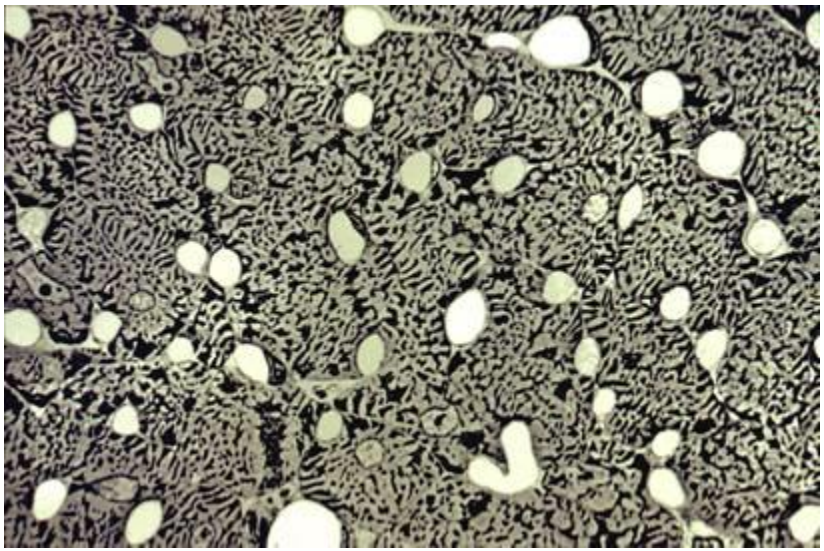


CKD patient

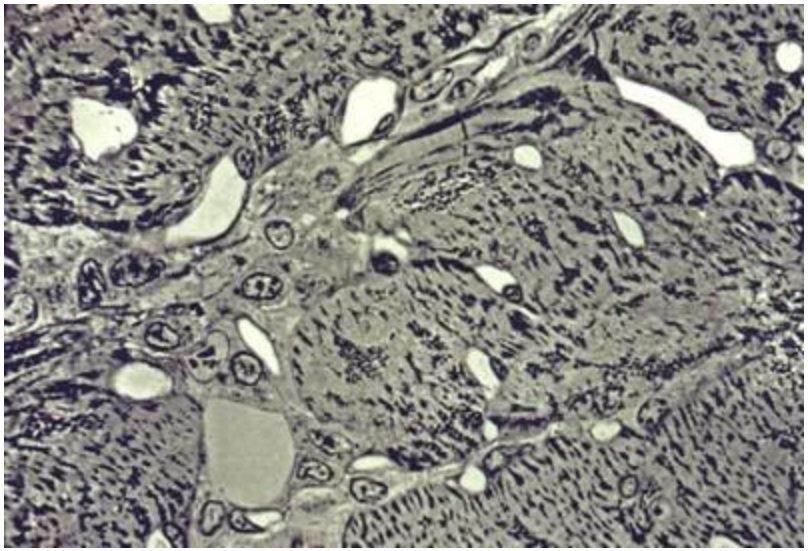


(Amann et al. JASN 1998)

Myocyte-capillary mismatch in experimental CKD



sham



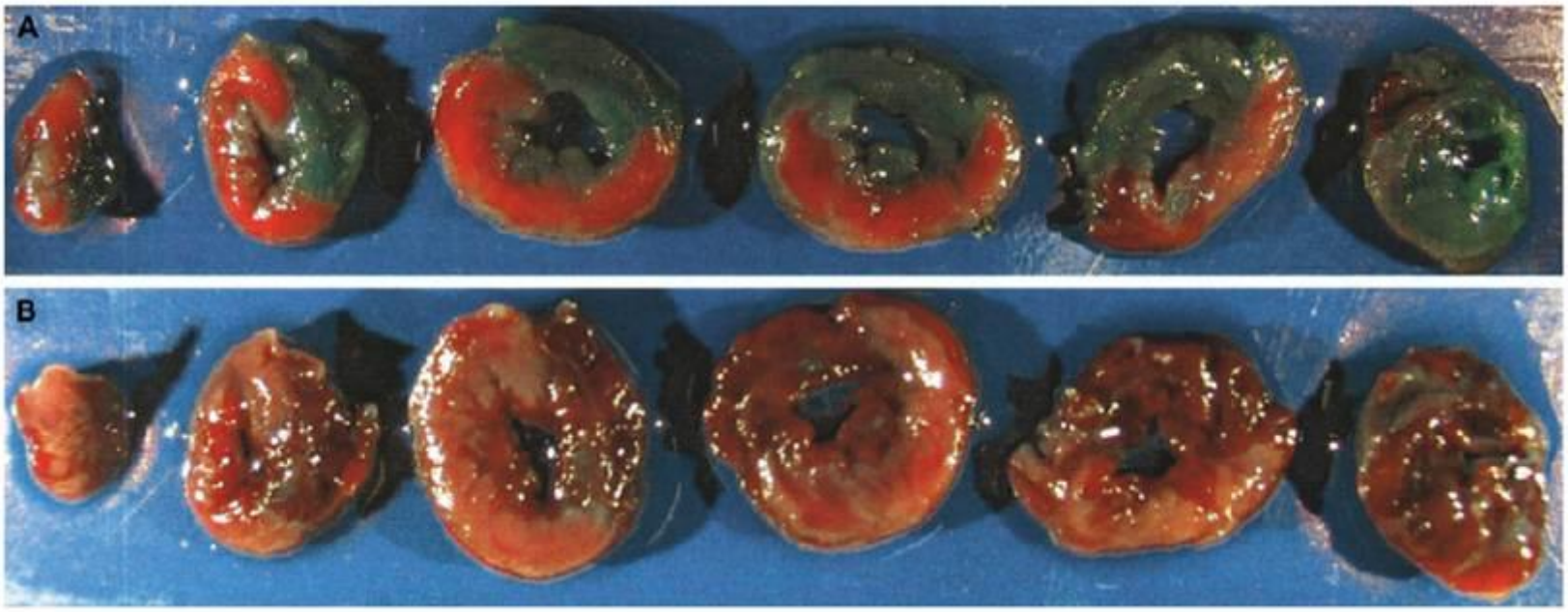
SNX

→ - 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

sham

SNX

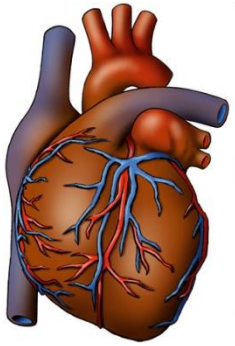


Area of infarction (in % LV) :

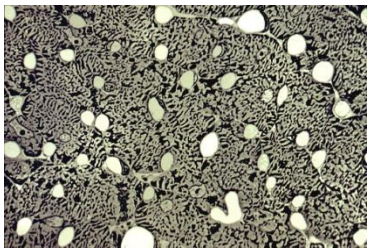
18.8 ± 6.6 % in sham
30.6 ± 6.7 % in SNX
($p<0.05$)

→ reduced myocardial ischemia tolerance in SNX !

Vascular maladaption in CKD under ischemic conditions

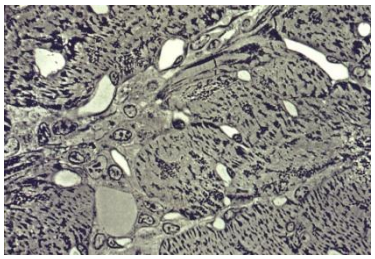


sham



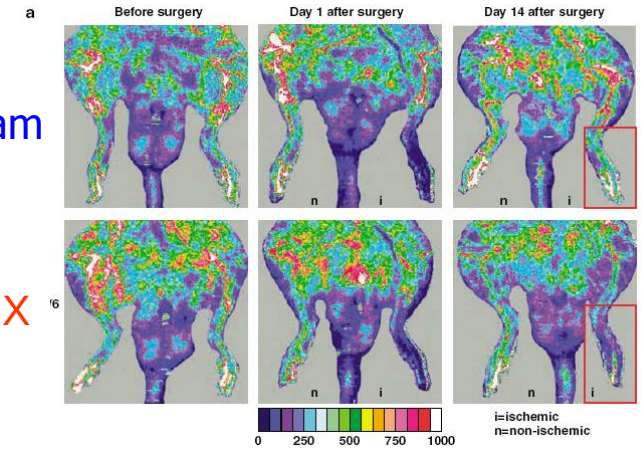
-25%

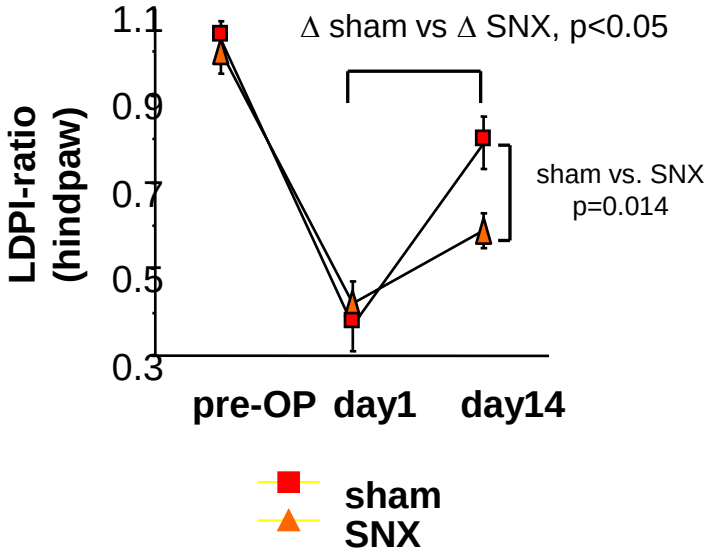
SNX



sham

SNX



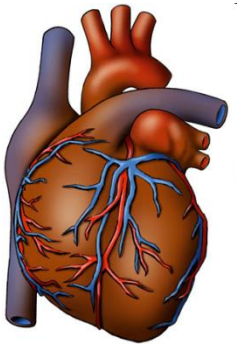


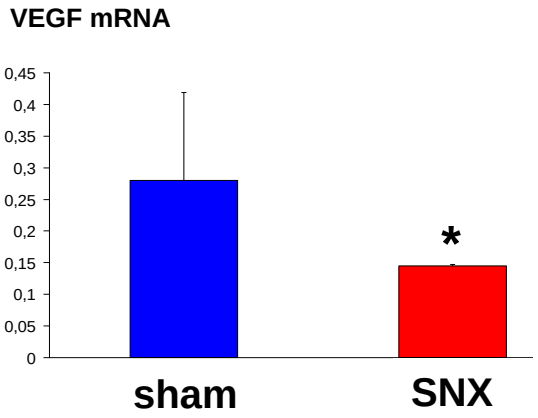
(Amann et al. 1992, 1996, 2000, Jacobi et al. 2005)

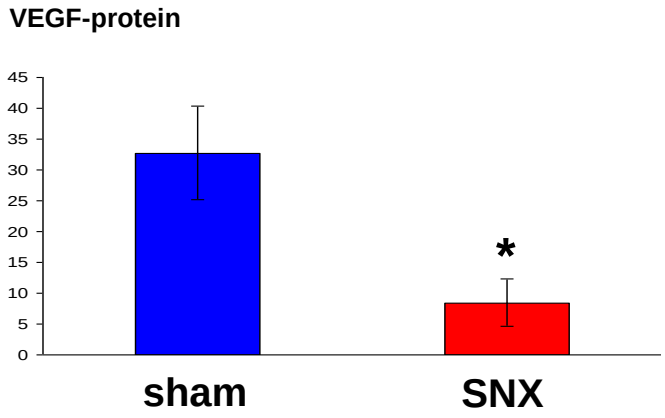
Lack of adaptive VEGF-regulation in CKD under ischemic conditions (LVH and hind-limb)

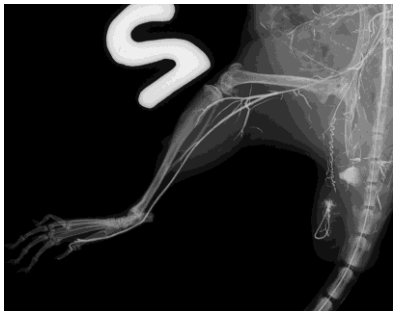
sham

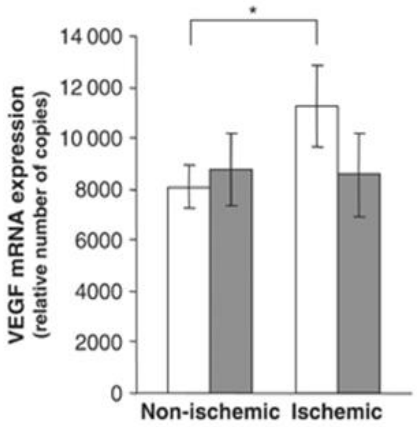
SNX

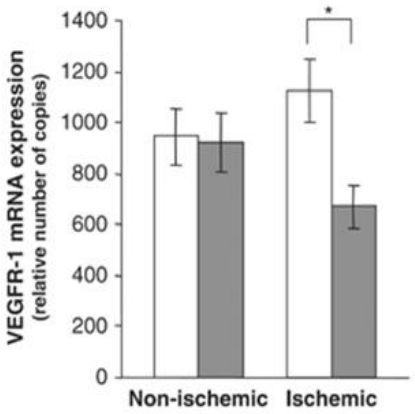


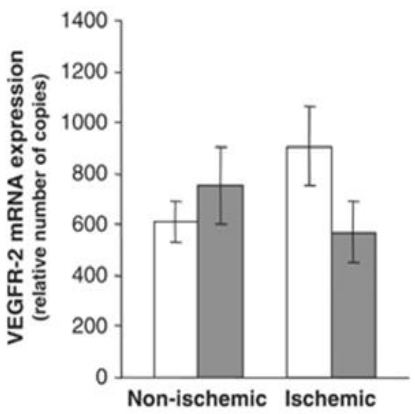






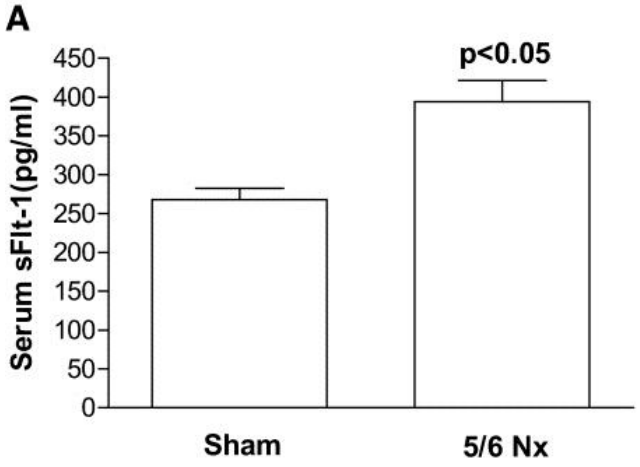


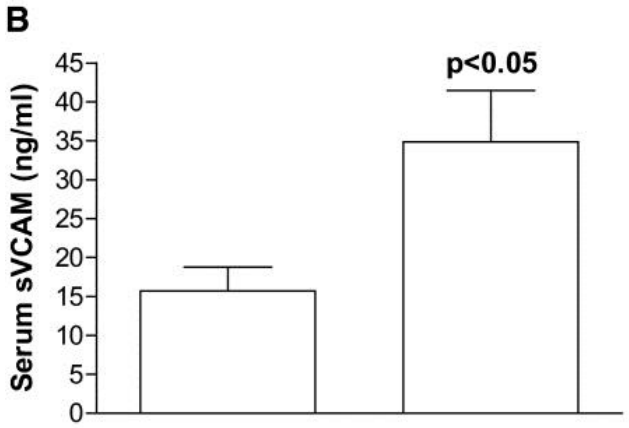


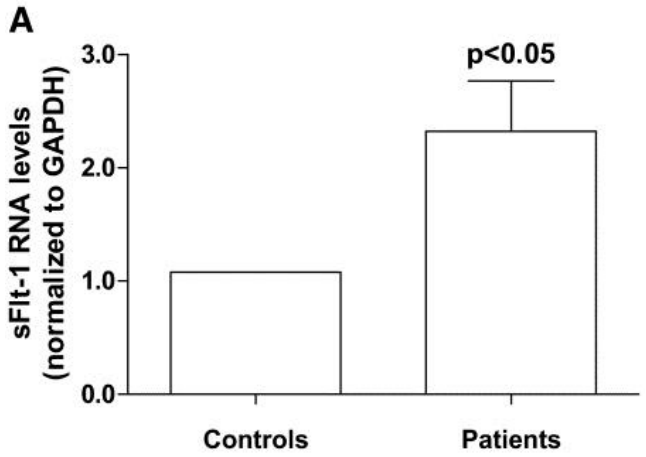


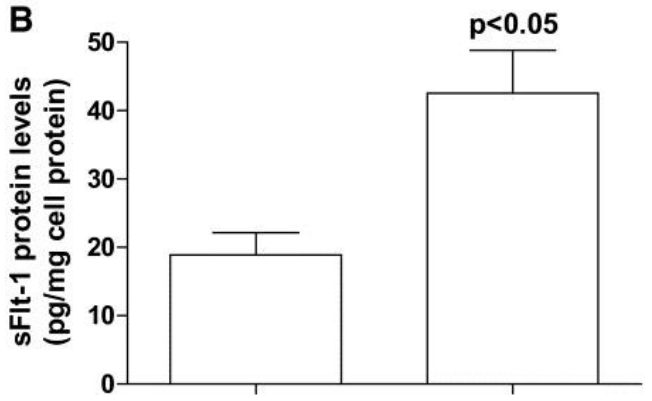
The Soluble VEGF Receptor sFlt1 Contributes to Endothelial Dysfunction in CKD

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









→ anti-angiogenic effect of CKD serum with ↑apoptosis of EC and ↓NO

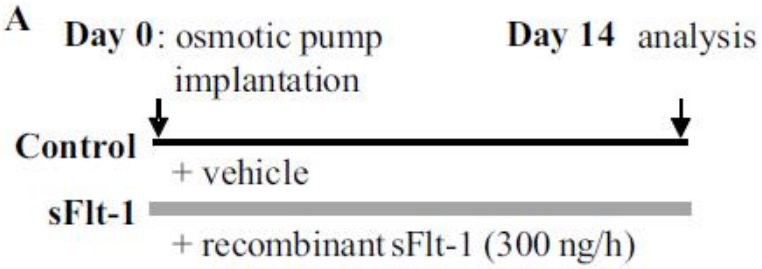
Basic Res Cardiol (2015) 110:30
DOI 10.1007/s00395-015-0487-4

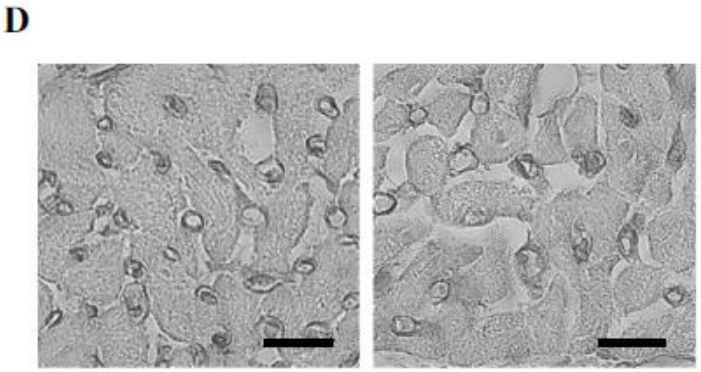
ORIGINAL CONTRIBUTION

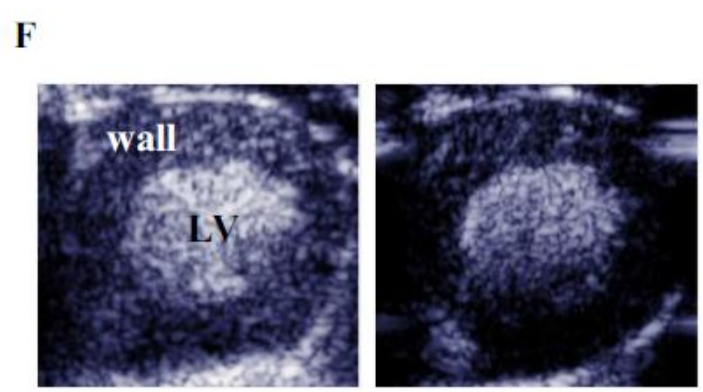
Soluble Flt-1 links microvascular disease with heart failure in CKD

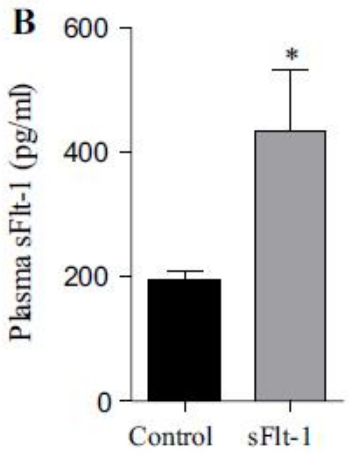
Giovana S. Di Marco[1] · Dominik Kentrup[1] · Stefan Reuter[1] · Anna B. Mayer[1] · Lina Golle[1] · Klaus Tiemann[2] · Manfred Fobker[3] · Christiane Engelbertz[4] · Günter Breithardt[4] · Eva Brand[1] · Holger Reinecke[4] · Hermann Pavenstädt[1] · Marcus Brand[1]

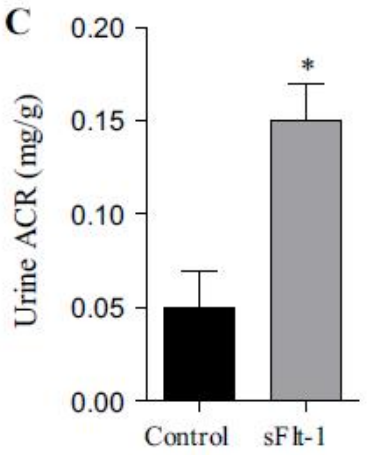
Elevated sFLT-1 levels reduce capillary density in the heart

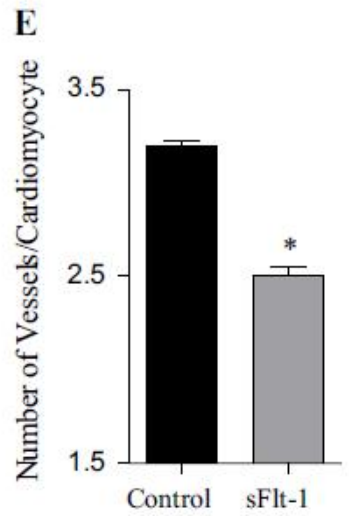


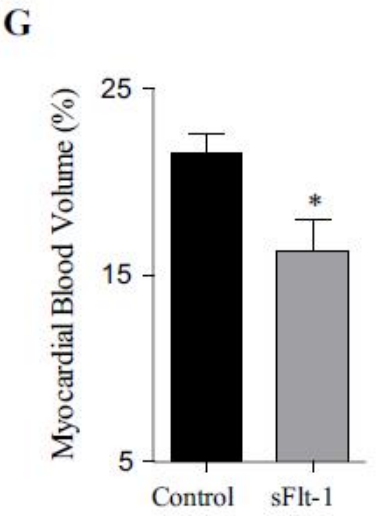










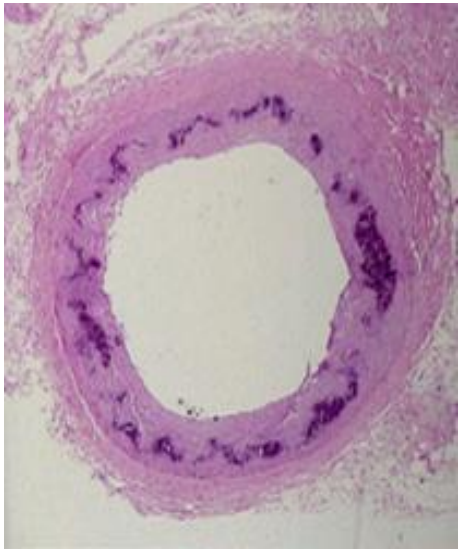


Cardiovascular pathology in CKD - crosstalk between kidney and cardiovascular system

- 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)**

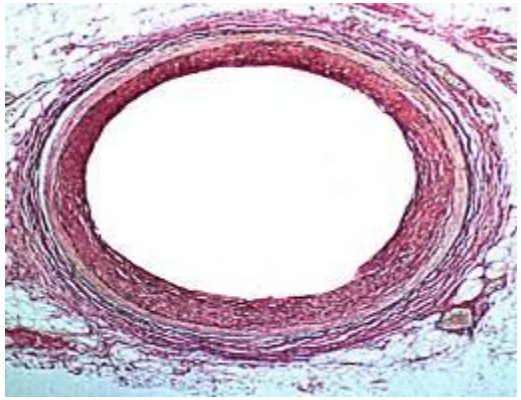
Accelerated arteriosclerosis in CKD - Uremic arteriopathy

fibrous or fibro-elastic intimal thickening

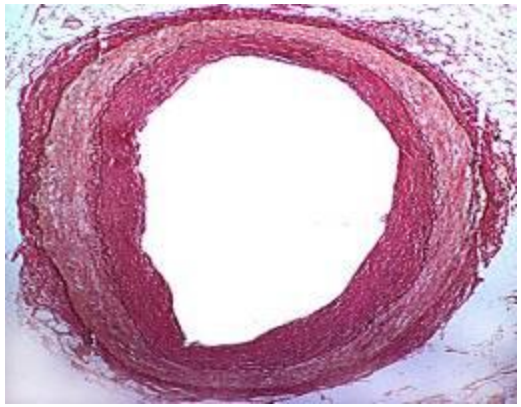


Epigastric artery of a 46y old patient at the time of renal transplantation

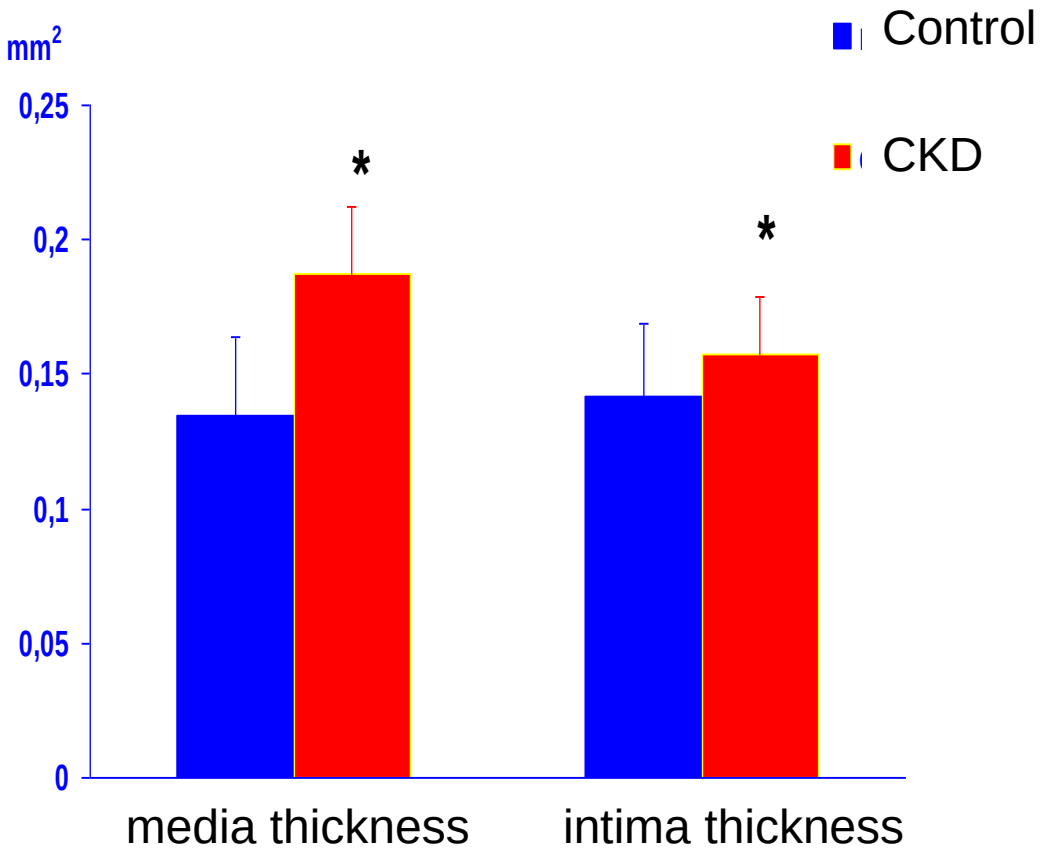
Wall thickening of coronary arteries in CKD



control



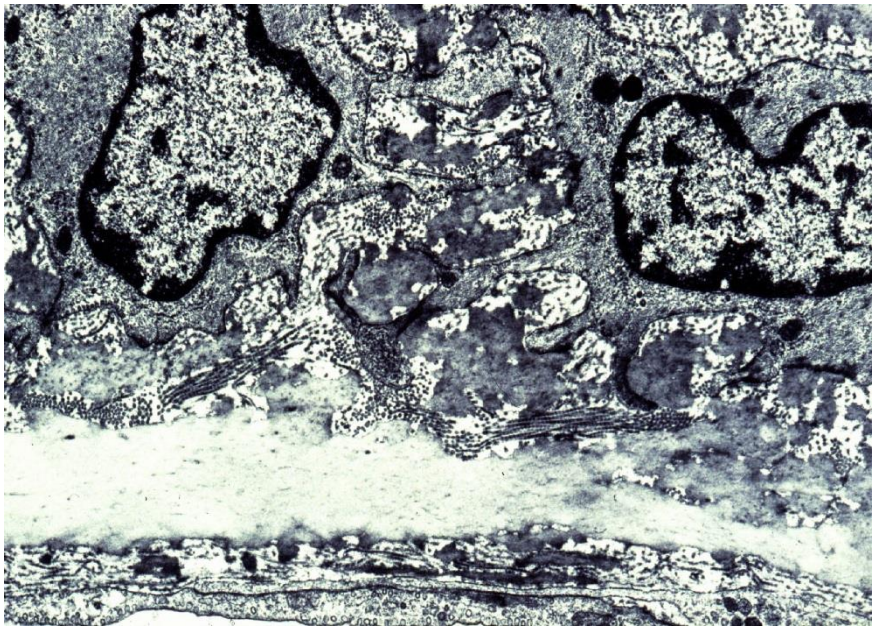
CKD



(Schwarz et al., NDT 2000)

Arterial wall thickening in CKD is acompanied by ultrastructural changes

Normal morphology of aortic media (sham)

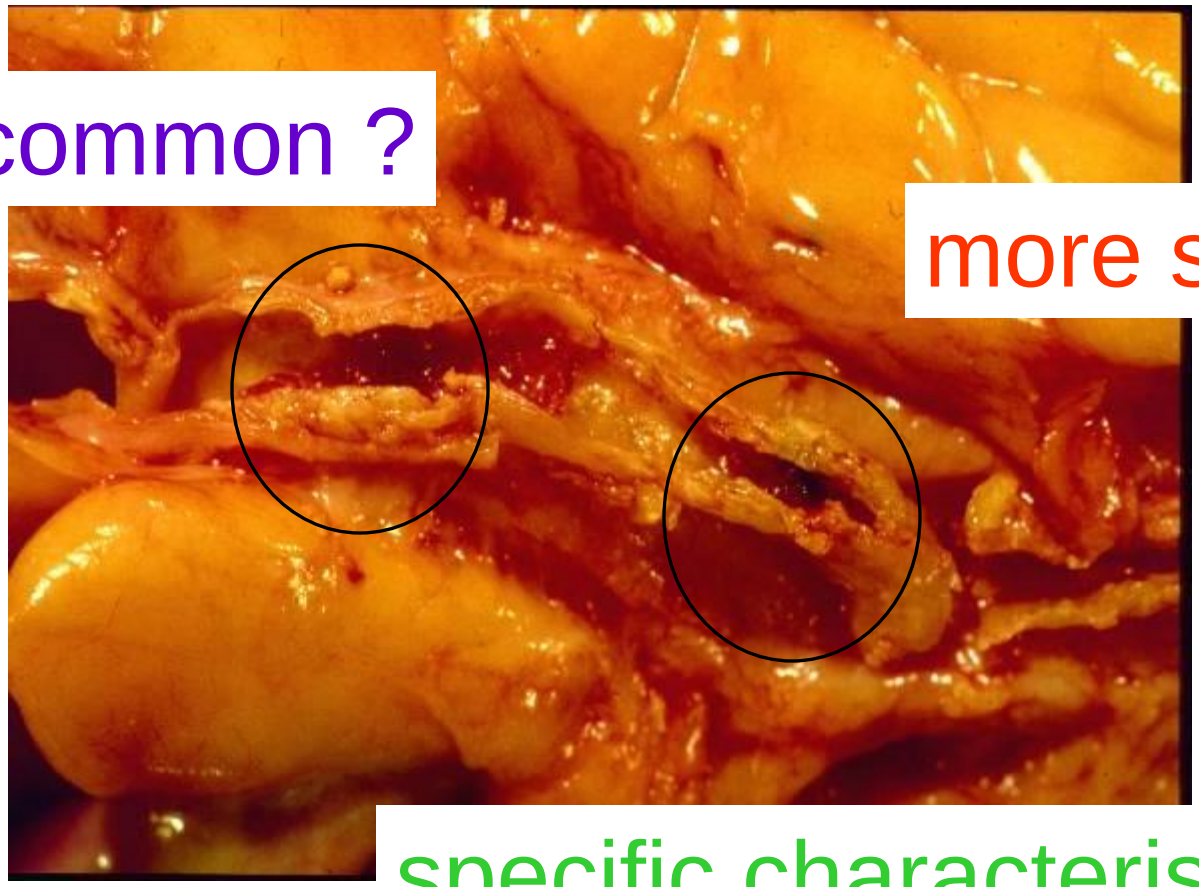


Media thickening with hyperplasia of VSMC, increased ECM and reduced elastic fibre content

→ reduced vascular elasticity, increased vascular wall stiffness, RR ↑, LVH ↑ , calcification ↑

Atherosclerosis in CKD ?

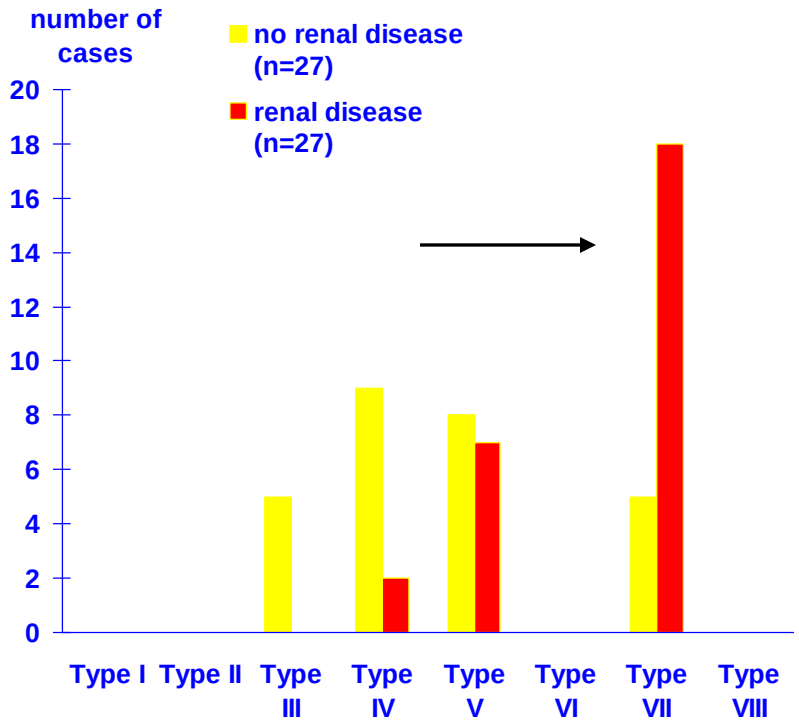
more common ?

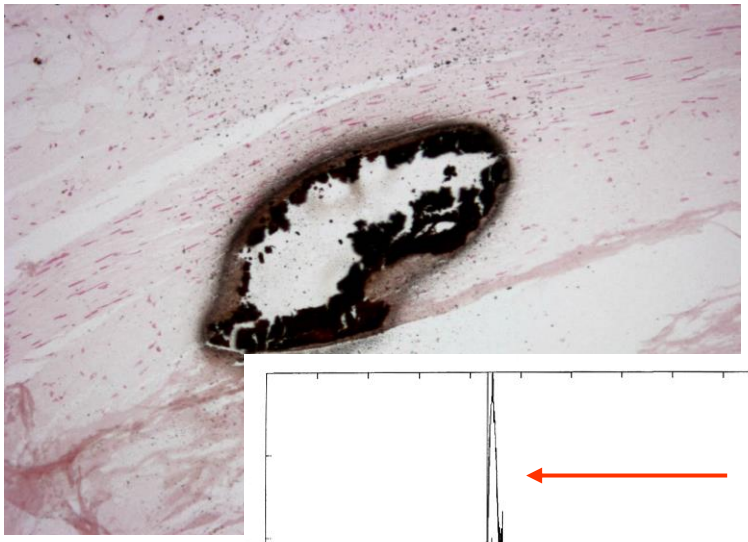


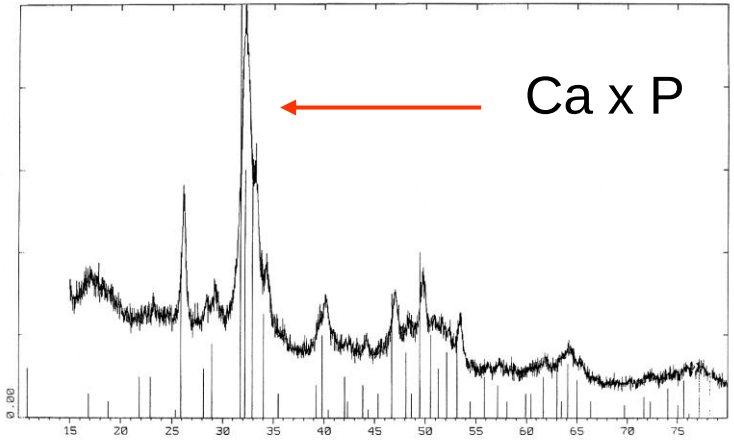
more severe ?

specific characteristics ?

Atherosclerosis in CKD







X-ray diffraction analysis of

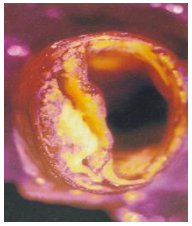
→ pro-inflammatory phenotype of atherosclerotic plaques in CKD !

Cardiovascular pathology in CKD

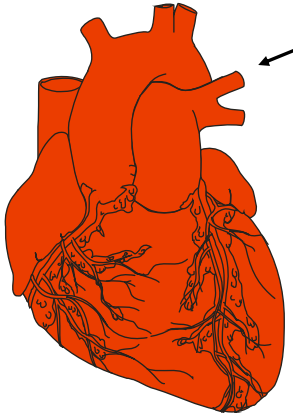
LVH

atherosclerosis

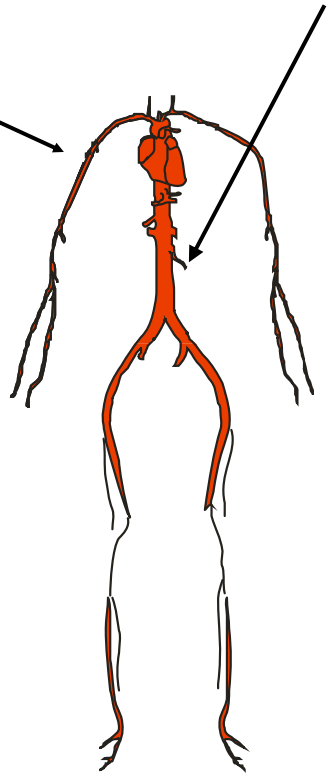
calcification

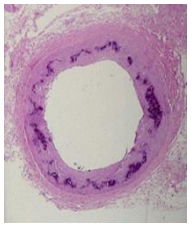


fibrosis



microarteriopathy

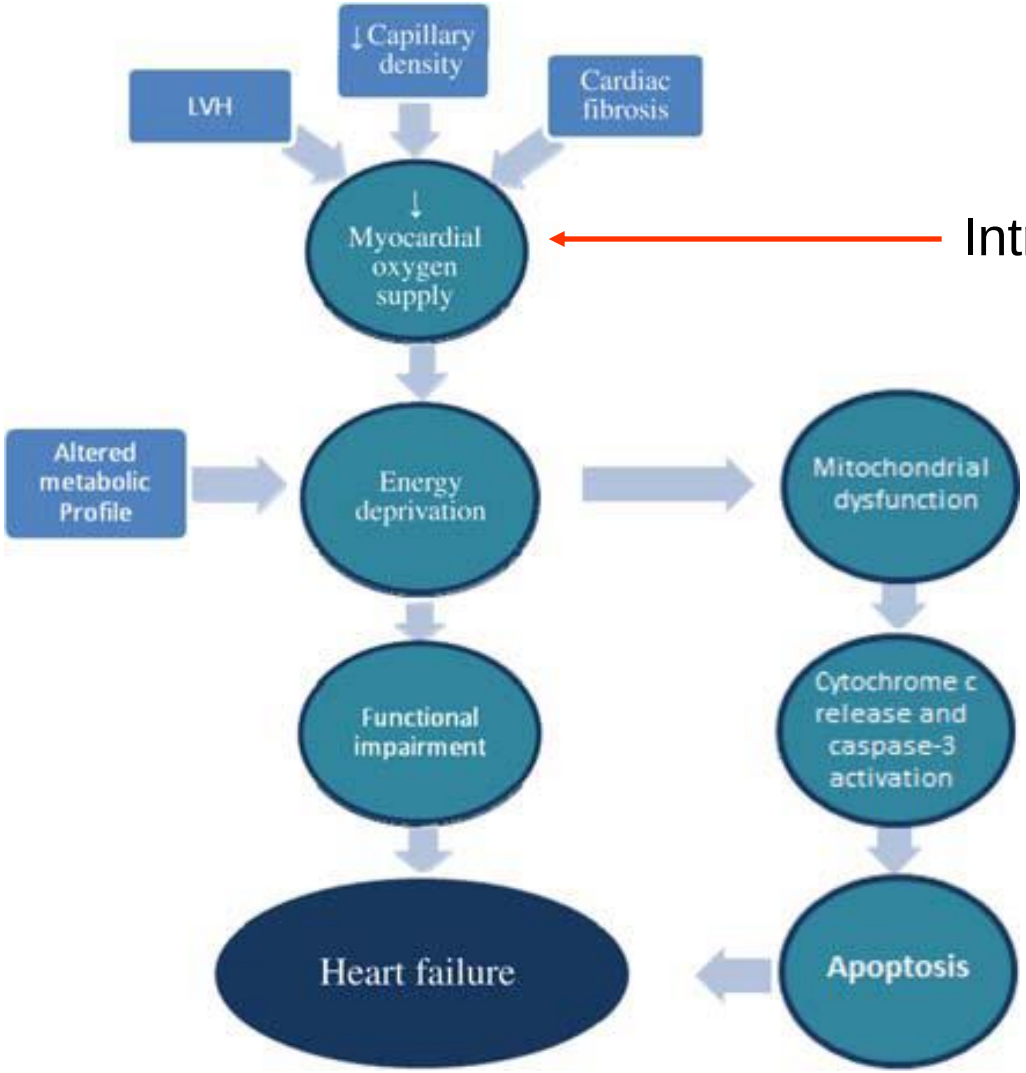




reduction in capillarisation

arteriosclerosis

Phenotypic alterations in uremia



(Smith et al. 2009)

The American Journal of Medicine (2006) Vol 119 (5A), 31S-39S

ELSEVIER

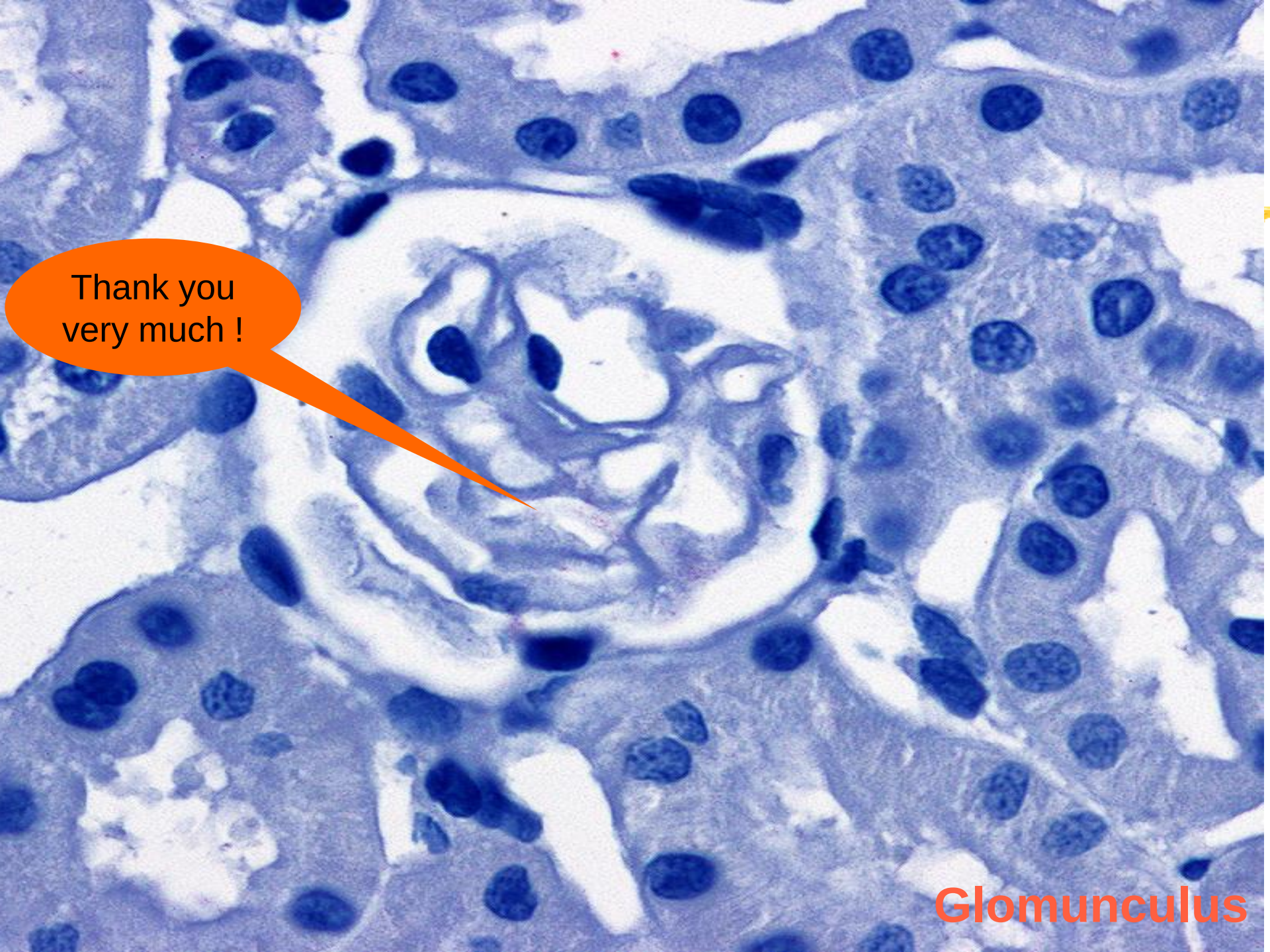
THE AMERICAN JOURNAL of MEDICINE®

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 !
Glomunculus