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Abnormalities of heart morphology at an early stage of renal disease – the role of oxidative stress.

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Even minor reduction of GFR causes not only accelerated coronary atherogenesis, but also cardiac remodeling and microvessel disease. Oxidative stress is one of the mechanisms causing such structural abnormalities. The current study in the apolipoprotein E -/- mouse was designed to investigate whether nephron reduction by uninephrectomy (UNX) causes cardiac remodeling and whether this is prevented by antioxidative treatment, comparing Tempol or Ebselen with the ACE inhibitor (Trandolapril).

ApoE knockout mice were randomized to undergo UNX or sham operation and subsequent treatment with either Tempol, Ebselen, Trandolapril, or a combination of Tempol plus Trandolapril. After 12 weeks the experiment was terminated by perfusion fixation. Quantitative morphologic analysis of the myocardium was performed. Additionally the expression of nitrotyrosine, eNOS, iNOS, TGF- β_1 , and its receptors, VEGF, flt-1, collagen I and IV, and MMP-1 was assessed using immunohistochemistry or Western blotting.

Untreated UNX animals had lower capillary length density and higher volume fraction of interstitial tissue in the myocardium and bigger plaques area in aorta compared to sham op. These changes did not develop in UNX animals treated with Tempol, Ebselen, Trandolapril, or Tempol + Trandolapril. In untreated UNX compared to sham op the expression of nitrotyrosine, TGF- β_1 , VEGF, and collagen I was more marked, and this was ameliorated by Tempol, Ebselen, Trandolapril, and Tempol + Trandolapril.

Remodeling of the heart muscle in the ApoE -/- mouse starts to develop even after minor reduction of renal function by uninephrectomy. Oxidative stress is likely to be an important mechanism inducing cardiac remodeling in kidney diseases and reduction of oxidative stress (in this study by Tempol or Ebselen) may prevent heart remodeling comparable to ACE inhibition. Effective antioxidant therapy may slow down progression of atherosclerosis. Combination of an ACE inhibitor with antioxidant had no additional beneficial effect in this study.