Nadezda Koleganova
Dr.med.

**Heart and vascular remodelling in uremia – prevention with calcimimetic R-568 and calcitriol.**

Geboren am 30.05.1977 in Ashgabat, Turkmenistan
(Staats-) Examen am 30.06.2001 an der turkmenisches staatliches medizinisches Institut, Ashgabat, Turkmenistan

Promotionsfach: Innere Medizin
Doktorvater: Prof. Dr. Dr. med. h. c. mult. Eberhard Ritz

Renal insufficiency increases the cardiovascular risk, accelerates atherogenesis, and causes vascular wall remodelling. Structural remodelling of the heart in patients with chronic renal failure comprises left ventricular hypertrophy, myocardial fibrosis, and capillary/myocyte mismatch leading to a microvascular deficit. Although calcimimetics typically act by lowering serum parathyroid hormone (PTH) levels, potential direct action of calcimimetics on the vasculature cannot be excluded because of the presence of calcium sensing receptors in vascular walls.

It was the purpose of the present study to compare the effects of the calcimimetic R-568 with those of calcitriol on interstitial fibrosis and the microvascular deficit in the heart. The signalling mechanisms involved were investigated. Furthermore, the effects of the calcimimetic R-568 and those of calcitriol on vascular structure were evaluated.

Three-months-old male Sprague-Dawley rats underwent subtotal nephrectomy (SNX) or sham operation and were observed for 90 days. Subsequently, the animals received R-568 (17 mg/kg/day), calcitriol (135 ng/kg/day), or vehicle. At sacrifice, organs were harvested using pressure-controlled perfusion fixation. Stereologic parameters (capillary length density [Lv] and volume density of the interstitial tissue [Vv]) of the heart were quantified. The morphologic parameters of vessels (wall thickness, and wall to lumen ratio) were quantified in the aorta and carotid arteries.In addition, the expression of signalling molecules, of the calcium sensing receptor (CaSR), and of the vitamin D receptor (VDR) protein were assessed using immunohistochemistry and Western blotting.

Residual kidney function was comparable in all SNX groups. *Cardiac hypertrophy* (heart to body weight ratio) was not affected by R-568 or calcitriol treatment. The *capillary length density* was lower in the vehicle treated SNX compared with the sham-op, and this was prevented in SNX treated with R-568 or calcitriol. Myocardial remodelling in SNX was associated with higher expression of *TGF-β, VEGF, ET-1*, and *nitrotyrosine*, which were less abundant in SNX treated with R-568 or calcitriol. Treatment with R-568 resulted in higher abundance of phosphorylated *ERK-2* and treatment with calcitriol increased total ERK-2 expression in myocardium.*CaSR* protein expression in cardiomyocytes and the aortic intima was not different between SNX and sham-op. CaSR protein expression was significantly higher in both SNX and sham-op treated with R-568 compared with their respective controls and with calcitriol-treated animals. *Aortic* and *carotid wall thicknesses* were higher in vehicle treated SNX compared to sham-op. This was prevented by the treatment with R-568 but not with calcitriol. In addition calcitriol (but not the calcimimetic) promoted calcification of the vessel wall. The number of *PCNA*-positive cells in the intima and media was significantly higher in SNX treated with calcitriol compared with any other group.

The microvascular deficit in a model of uremic cardiomyopathy was attenuated by the calcimimetic R-568, as well as by calcitriol (both of which lowered PTH). In parallel both interventions reduced interstitial fibrosis and indicators of oxidative stress. The findings argue for causal role of PTH in the genesis of uremic cardiomyopathy.In contrast to calcitriol, the calcimimetic R-568 attenuated vascular remodelling and neointimal hyperplasia in the aorta and carotid artery of uremic rats. Calcitriol treatment of uremic animals was also associated with increased endothelial and smooth muscle cell proliferation as well as calcification of the vessel wall.These data suggest a role of calcimimetics in the treatment of cardiomyopathy and vascular remodelling in uremia. The effects of the calcimimetic on the vessel wall are more favourable than those of calcitriol.