# 8 Summary


## Adventitial $VEGF_{165}$ gene transfer induces positive remodeling and prevents luminal loss after experimental balloon angioplasty in porcine coronary arteries

**Background:** Negative arterial remodeling is known to play an important role in the pathogenesis of restenosis after PTCA. Previous studies have shown that coronary balloon angioplasty induces adventitial microvessel (*Vasa vasorum*) angiogenesis, and that the regression of these adventitial microvessels coincides with negative arterial remodeling leading to arterial lumen loss. These findings suggest that increased angiogenesis and delayed/inhibited regression of injury-induced microvessels may reduce (or even prevent) negative remodeling. As experimental studies have provided evidence that neovascularization within the atherosclerotic plaque may enhance plaque progression, trials on „therapeutical" angiogenesis should address rather the adventitia than the tunica intima or media of the artery.

**Objective:** This study examined the effect of local (peri)adventitial vascular endothelial growth factor ($VEGF_{165}$) gene transfer on vascular thickening, adventitial microvessel angiogenesis/regression, and arterial remodeling after balloon injury-induced lesion formation in porcine coronary arteries. Moreover, lesions were examined for total collagen, elastin, and $\alpha$-actin content and macrophages/T cell density.

**Methods:** 20 pigs underwent balloon injury in two major coronary arteries, followed by plasmid liposome gene transfer with either $VEGF_{165}$ or control gene LacZ (50 µg of DNA with 50 µg of Lipofectine) into the (peri)adventitial space using a needle injection catheter. Coronary arteries were examined at days 1, 7, 14, and 28 (n = 5 per group) after dilation/gene transfer using morphometrical analysis of digitized images, immunohistochemistry, histochemistry, RT-PCR, and *in situ* hybridization.

**Results:** The mean Intima+Media (I+M) area increased after angioplasty in both treatment groups equally and showed no significant difference neither in dimension nor in I+M microvessel density, I+M inflammatory cell density, or I+M matrix composition. At days 14 and 28, VEGF treated arteries showed significant positive remodeling and accordingly less lumen area loss compared to LacZ treated arteries (lumen loss day 14 - VEGF: 5.09 % ± 7.5; LacZ: 40.13 % ± 2.93. lumen loss day 28 - VEGF: –5.35 % ± 18.33; LacZ: 49.04 % ± 1.64. $P < 0,05$). The lumen

area preservation in the VEGF group was associated with significant higher densities of adventitial microvessels, endothelial cells, T cells and elastin, and less contractile myofibroblasts at days 14 and 28 after intervention. No statistcally significant differences were observed regarding the adventitial area and the macrophage density. Collagen content differed significantly only at day 14, at day 28 there was only a trend towards increased adventitial collagen in the VEGF treated group.

**Conclusions:** In this porcine model of coronary artery injury, needle injection catheter mediated $VEGF_{165}$ gene transfer into the outer compartment of the artery was safe in terms of unwanted lesion progression as the procedure neither enhanced I+M growth or vascularization nor caused any changes in I+M matrix composition. The locally restricted, (peri)adventitial delivery of $VEGF_{165}$ gene induced neovascularization in the adventitia, prevented the anticipated adventitial microvessel regression, and reduced lumen area loss due to distinct positive remodeling. The enlargement of the artery was associated with a significantly elevated adventitial microvessel and endothelial cell density, suggesting improved tissue oxygenation and conceivably increased local nitric oxide (NO) availability as modulators of arterial remodeling. Adventitial elastin accumulation associated with a reduced amount of contractile cells in the adventitia might play a functional role in the development of positive arterial remodeling.