Retrograde Liposomal eNOS S1177 D Transfection Increases Myocardial Function in a Porcine Model of Chronic Myocardial Ischemia

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eNOS activation is an essential signal of the VEGF mediated cardioprotection. In a previous study local application of eNOS S1177D (a constitutive active mutant of eNOS) was sufficient to attenuate acute ischemia/reperfusion injury in pigs. We now investigated in a pig model of chronic myocardial ischemia whether an eNOS S1177D transfection has a pro-angiogenetic effect in the hibernating myocar-

dium. **Methods:** A reduction stent was implanted in the LAD, to induce a high-grade stenosis. After 28 days (hibernating myocardium) the pigs were treated retrogradely with either saline solution (group A, n = 6) or eNOS cDNA (group B, n = 6). For group C (n = 3) the protocol of group B was used with additional oral application of the NO-inhibitor *L*-NAME (500 μ*M*). Regional myocardial blood flow (microspheres) was examined at day 28 and day 49, regional myocardial function was assessed at day 49 (subendocardial segment shortening, displayed as % of RCx- region). **Results:** At day 49, the number of visible collateral arteries was higher in group B (4.3 ± 0.38; $p < 0.05$) compared with group A (1.5 ± 0.4) and C (2.5 ± 0.3). Accordingly, increased capillary density was found in group B (B: 81.78 ± 7.48% vs. C: 67.28 ± 6.61% of Cx-area; $p < 0.05$). The regional myocardial blood flow showed no differences between the groups at day 28 in the LAD-perfused area. At day 49 the regional blood flow increased in the LAD-territory in group B (70.9 ± 6% of Cx) compared to group C (45.6 ± 4.6% of Cx). In the distal LAD area, regional segment shortening was reduced in group A (22.8 ± 8.1% of Cx). This loss of function was improved in group B (44.1 ± 6%; $p < 0.05$), but not in group C (18.7 ± 3.4%). **Conclusion:** We demonstrated for the first time that retrograde liposomale eNOS S1177D transfection induces a functionally relevant neovascularisation in a model of hibernating myocardium.