IMPROVED LIMB PERFUSION AND VASCULOGENESIS AFTER INTRAMUSCULAR INFUSION OF ERYTHROPOIETIN IN AN EXPERIMENTAL MODEL OF LIMB ISCHEMIA

ACC Poster Contributions
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Background: Erythropoietin (EPO) has been shown to enhance angiogenesis, but its precise mechanisms of enhancement during ischemia are not fully elucidated. The angiopoietin (Ang)/Tie system has been reported to be critically involved in disease progression through the activation of signaling pathways that control angiogenic remodeling and Ang-1 and Ang-2 activation.

Methods: Wild type C57BL/6 male mice underwent unilateral hind-limb ischemia and were subsequently divided in two groups and received either EPO or normal saline intramuscularly (im). At day 28 they were sacrificed and quantitative real time RT-PCR was performed to the muscle tissues from both limbs to analyze the differential gene expression of vascular endothelial growth factor (VEGF), Tie-2, Ang-1 and Ang-2. Mice underwent Laser Doppler perfusion imaging after surgery on days 1, 7 and 28 for the estimation of the bilateral hind-limb perfusion. Muscle tissue sections were stained with rat anti-CD31 antibody. Capillaries and arterioles in the ischemic areas were counted with confocal microscopy at day 28.

Results: Ischemic/non-ischemic ratio was significantly increased in ischemic limbs of EPO-treated mice versus control mice at 7 days (p<0.014 vs control for EPO), which was maintained at 28 days (p<0.05 vs control). Capillary density was increased in the EPO-treated group compared to control (1.92±0.95 vs 0.71±0.59 cap/cm² p<0.05). The expression of Ang-2, Tie-2 and VEGF in the ischemic limbs of the Epo-treated group was significantly increased compared to the control group (p<0.05 vs control). In contrast, the Ang-1 expression didn’t significantly differ between the two groups. Conclusion: Erythropoietin treatment improves perfusion in both limbs, promotes vasculogenesis and increases neoangiogenesis by upregulation of the Ang-2/Tie-2 pathway and down regulation of Ang-1. These finding suggests that erythropoietin may play a critical role in neoangiogenesis by interfering with the local expression of angiogenic factor.