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SUPPLEMENTAL OXYGEN CONTROLS SMOOTH MUSCLE CELL PROLIFERATION AND ANASTOMOTIC INTIMAL HYPERPLASIA AT IN ARTERIOVENOUS FISTULAS IN RABBITS

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Background The number of patients with end-stage renal disease (ESRD) continues to rise in the world. About 39% prevalent haemodialysis patients underwent creation of arteriovenous fistulas (AVF) as the primary vascular access in more than 400 000 patients in 2004, and it is estimated that 50% of AVF failures are due to anastomotic intimal hyperplasia (AIH). We suspected that the hypoxia happened in the local lumen is the main reason that lead to the AIH.

Methods 52 New Zealand white rabbits, four in each group, were assigned to one of the four following arms of the study: control, surgery with supplemental oxygen, without oxygen and sham group. An arteriotomy was created in the common iliac artery and the vein anastomosed in a side-to-side manner and treated for 1, 3, 7 and 21 days in 21% or 30% oxygen environment.

Results We speculated that creation of an AVA results in artery wall hypoxia and increase the HIF-1α expression in the local wall after 7 and 21 days. Supplemental oxygen administered for 7 and 21 days immediately following creation of an AVA will increase artery wall oxygen concentration, inhibited HIF1-α gene expression, and reduced RSMC proliferation. These changes may be dependent on altering levels of oxidative stress. The VEGF secretions were higher in 3 and 7 days with surgery and without oxygen treated, which means VEGF played the key role in the plasma led to SMC proliferation. We still found VEGFR2 high expression in the AV anastomosis in 3, 7 and 21 days without oxygen, and expression on 7 days were more significant compared with normoxia group. We also used VEGFR2 antagonist Tryphostin to block the receptor and observed that the inhibition of RASMC proliferation in hypoxia (5%) was not as obvious as in normoxic condition, because increase in VEGF secretion was dependent on HIF-1α and VEGFR2 expression was also enhanced in hypoxic condition. We found that supplemental oxygen increased VEGFR2 expression in RASMC in vitro which suggested that autocrine regulation via increased levels of VEGF and its receptor plays a role in the proliferation of RASMC under hypoxia condition. We still speculated VEGF combined with VEGFR2 and activated ERK and Akt signalling to enhance the RASMC proliferation in vitro and in vivo.

Conclusion The AVF patients expected to be provided an inexpensive, safe, simple and effective method to control intimal hyperplasia at the site of an AVA. We suggest the short-term administration of supplemental oxygen could inhibit HIF-1α and VEGF signalling to reduce the AIH in the local blood vessel.