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REGULATION OF TRANSFORMING GROWTH FACTOR β1 SIGNALLING IN THE POST-ISCHAEMIC MOUSE HEART

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Objectives eNOS-derived NO induces acute phase tissue hyperoxia in vivo and hyperoxia induces fibroblast trans-differentiation in vitro. However, little is known about the effect of reperfusion-induced hyperoxia on myocardial infarct healing. The current study is to determine how late phase reperfusion hyperoxia and NO regulate cardiac myofibroblast formation.

Methods C57BL/6 wild-type, eNOS$^{-/-}$ and iNOS$^{-/-}$ mice were subjected to 30-min LAD occlusion followed by 14-days of reperfusion. Myocardial tissue PO_2 was monitored with electron paramagnetic resonance oximetry. Protein expression of TGF-beta1, p-Smad2/3, t-Smad2/3, p21 and α-SMA were measured with ELISA and western blot.

Results There was an acute phase overshoot of tissue Po_2 in the WT and iNOS$^{-/-}$ but not eNOS$^{-/-}$ mice. After 60 min reperfusion, tissue hyperoxia was observed in all three groups and peaked at day 3 with significantly lower PO_2 in the eNOS$^{-/-}$ mice than that in the WT and iNOS$^{-/-}$ mice (22.4±0.8 vs 39.8±1.13 and 26.9±1.3 mm Hg). Protein expression of the total and active TGF-β1, p-Smad2/3 over t-Smad2/3 ratio, p21 and α-SMA were significantly increased after reperfusion in the WT mice. Knockout of eNOS or iNOS further increased the expression of these signals. Immunohistochemical staining indicated the expression of α-SMA in the infarct area. Immunoprecipitation demonstrated the nitration of TGF-β RII. Carbogen (95% O_2+5% CO_2) treatment increased the expression of p-Smad2/3 over t-Smad2/3 which was inhibited by EUK134 (10006329 EUK 134) and sodium nitroprusside.

Conclusions Late phase reperfusion tissue hyperoxia promoted while eNOS-/iNOS-derived NO/$ONOO^-$ inhibited cardiac TGF-β1 signalling and myofibroblast trans-differentiation. These findings may provide new targets to improve myocardial infarct healing and repair.