[gw22-e0229]

LONG-TERM ENHANCED EXTERNAL COUNTERPULSATION DOWNREGULATES THE HIF-1A EXPRESSION OF VASCULAR ENDOTHELIAL CELLS IN ATHEROSCLEROTIC PIGS

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10.1136/heartjnl-2011-300867.154

Objectives Mechanisms underlying the beneficial effect of Enhanced External Counterpulsation (EECP) in atherosclerotic diseases are not well defined. Since hypoxia-inducible factor-1α (HIF-1α), as a novel transcription factor, has recently been believed to play a pivotal role in the pathogenesis of atherosclerosis, we hypothesised that long-term EECP could downregulate the expression of HIF-1α in vascular endothelial cells of atherosclerotic lesions, contributing to its clinical outcomes. We studied this hypothesis in a porcine model of atherosclerosis.

Methods Eighteen twenty-day-old male domestic pigs were randomly assigned into three groups: the normal control group (normal group, n=6), the hypercholesterolemic control group (HC group, n=6) and the hypercholesterolemic +EECP group (EECP group, n=6). Pigs in normal group were fed with normal chow diet, while the pigs in the other two groups were fed with cholesterol-rich chow diet in order to induce atherosclerosis. Six pigs in EECP group were anesthetised by intramuscular injection of 846 mixture and intravenous infusion of pentobarbital sodium. The EECP procedures were performed on them for 2 h every two days with 0.035 MPa/cm^2 pressure, summed total 36 h. After the end of EECP, all the pigs were sacrificed by injecting overdose of 10% potassium chloride into the heart. For each animal, the thoracic aorta was isolated for harvesting vascular endothelial cells (VECs) with collagenase I. One half of the harvested VECs were fixed with 4% paraformaldehyde and further embedded with paraffin. The remained VECs were prepared for extracting their total mRNA. Immunocytochemical staining for HIF-1α was performed on paraffin-embedded VECs, while RT-PCR was applied for detecting the transcriptional expression of HIF-1α, respectively.

Results The staining-positive rate of HIF-1α of aortic VECs in EECP group was much lower than that in HC group ((206±18)‰ vs (303±16)‰, p<0.05), but still higher than that in normal group significantly ((206±18)‰ vs (158±32)‰, p<0.05). In consistence with the result of immunochemical staining analysis, the relative ratio of RT-PCR products of HIF-1α, were lower in EECP group than that in HC group ((1.06±0.18) vs (1.59±0.22), p<0.05), but still higher than that in normal group significantly ((1.06±0.18) vs (0.77±0.18), p<0.05). The immunocytochemical expression of HIF-1α correlated positively to its relative ratio of RT-PCR products (r=0.768, p<0.05).

Conclusions HIF-1α may play an important role in atherogenesis. Transcriptional downregulation of HIF-1α may be one of the molecular mechanisms contributing to the clinical outcomes following EECP performation.