CARDIOVASCULAR RISK OF RECOMBINANT HUMAN ERYTHROPOIETIN APPEARS IN TRAINED RATS WITH ENDOTHELIAL NO SYNTHASE INHIBITION
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Chronic administration of recombinant human erythropoietin (rHuEPO) can generate serious cardiovascular side effects. rHuEPO, by modulating endothelial function, increasing erythrocytose, blood viscosity and shear stress on the vascular surface can be responsible of arterial hypertension (HTA) and thrombosis. Nitric oxide (NO), once released by endothelial cells can protect from cardiovascular noxious effects induced by chronic administration of rHuEPO. On these bases, we studied the cardiovascular effects of a chronic administration of rHuEPO in trained rats presenting an endothelial NO-dependent dysfunction. Rats were treated or not with rHuEPO (100 UI/kg, twice a week, subcutaneous injection) and/or an inhibitor of the endothelial NO synthase (eNOS) (10mg/kg/day of L-NAME) during 6 weeks. During the same period, the rats were subject to a treadmill exercise (5 days/week, 60 min/day).

The blood pressure was measured weekly. At the end of the experimental period, an endurance test was made. After sacrifice of rats, the citrate synthase activity was measured at the soleus muscle. The vasodilatory response to acetylcholine and the arterial morphology of isolated perfused and pressurized mesenteric small arteries were investigated. Capillary-to-fibre ratio (C/F) at the soleus muscle was studied by immunohistochemistry. A severe systolic high blood pressure developed in trained rats treated with rHuEPO and L-NAME (> 220 mmHg) associated with a markedly decreased acetylcholine-induced vasodilatation in perfused and pressurized mesenteric small arteries. Furthermore, the arterial wall of these arteries showed an increased media thickness and cross-sectional area suggesting an arterial remodelling in order to counteract the rise in systolic blood pressure. The citrate synthase activity was significantly higher in the exercise groups than that in the sedentary groups (this activity was not modified by rHuEPO treatment and/or L-NAME). In the group L-NAME + rHuEPO + exercise rats, we observed a deterioration of the exercise endurance. This latter, by inhibiting the eNOS, would negatively act on the capillarisation at the soleus muscles. Furthermore, we observed that these L-NAME + rHuEPO + Exercise-induced hypertensive rats died during the exercise test or the recovery period (mortality 50%).

In conclusion, the rHuEPO seriously affects the physical performance and cardiovascular adaptative function in trained rats with eNOS blockade and markedly potentiates the cardiovascular risk, such as hypertension, in condition of endothelial dysfunction. These findings suggest that the use of rHuEPO in sport, in order to improve physical performance, represents a high and fatal risk factor, especially with pre-existing cardiovascular risk.

Keywords: Cardiovascular, Doping, Treadmill