Dear Sir,

Induced hypertension due to treatments with recombinant erythropoietin (rHuEPO) is with no doubt the most frequent and important side effect of this hormone therapy, capable of conditioning the therapeutic success in subjects affected by anemia from renal failure. Although different factors, among which the increase in hematic viscosity, are recognized as possibly responsible for the pressure rise which often goes along with rHuEPO treatment, up to now a reliable explanation of the pathogenetic mechanisms of hypertension induced by erythropoietin [1] is still missing. In previous investigations, through the evaluation of the changes brought about by the intravenous administration of rHuEPO on the pretibial flux by means of the Xenon 133 clearance, we showed the existence of a direct vasoconstrictive action exerted by erythropoietin on the compliance vasa [2]. The presence of endothelial receptors for the erythropoietin could give account of such action [3]. Furthermore, in our previous investigations as well as in other investigations [4], it was shown how the intravenous chronic treatment was able to change the plasma levels of endothelin-1, a substance produced by the endothelium, able to induce a high vasoconstriction. Yet, the plasma dosage of endothelin does not seem to correspond to the real activity of the vasal endothelium. Therefore, we wanted to use an experimental model based on the umbilical arteries, where the receptors for endothelin are to be found [5]. The arteries were quickly

![Fig. 1. Production of immunoreactive endothelin-1 (ir ET-1) in the umbilical artery: electrolytic solution (I); rHuEPO solvent (II); 30 U of rHuEPO (III).](image)

20 µl of solvent. Then, the 3 umbilical artery segments were kept for 10 min at 37°C, were weighed and the corresponding supernatant frozen at -30°C, the endothelin-1 was dosed with the RIA method (Amersham, UK). The results obtained from 25 umbilical arteries showed the presence of a significant increase in the concentration of endothelin-1 from the medium to...
which rHuEPO was added (fig. 1). Results are expressed as means ± SE and Student’s test was performed for all comparisons. Therefore, our study seems to confirm the possibility that the vasoconstrictive action played by erythropoietin might be caused by the stimulus exerted by the hormone on the endothelial cells to make them produce endothelin-1. Our method consisted in taking, soon after a natural delivery, 10 cm of the median part of the umbilical cord from which we immediately isolated the umbilical artery by means of a stereo microscope which was divided into 3 2-cm long segments. The 1st segment (I) was put in 1 ml of cold buffered electrolyte solution (4°C), the 2nd (II) was kept in a medium with buffered electrolyte solution plus 20 µl of rHuEPO solvent (human serum albumin 2.5 mg/ml; sodium 160 mM; chlorides 100 mM; citrate 20 mM), the 3rd (III) was put in 1 ml cold buffered electrolyte solution and 30 U of rHuEPO with

To sum up, our findings seem to confirm the possibility that various growth factors and cytokines may play an important effect on the regulation of the vascular tone – as it was also shown through the increase induced by interleukin-1 on the production of prostacyclines and nitric oxide [6]. Further investigations are required to better identify the vasoconstrictive mechanisms of recombinant erythropoietin and its action on all the factors able to modify the vascular reactivity.

References


Buemi/Morabito/Paelia/Allegra/Frisina/ Gemelli/Manganaro/Stelitano/Palmara
Erythropoietin and Endothelin-1