rHuEPO INDUCED-HYPERTENSION LEADS TO EARLY RENAL DAMAGE

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INTRODUCTION AND AIMS

The introduction of recombinant human erythropoietin (rHuEpo) improved the treatment of anemia in chronic kidney disease patients.

However, in the recent years, some concerns were raised about this therapy, namely the development of cardiovascular complications, one of the major causes of death in these patients.

Hypertension development is closely associated with renal deterioration and is one of the most described side effects associated with rHuEpo therapy.

The aim of this study was to assess the effect of rhEPO-induced hypertension on renal function and lesions, using an animal model.

METHODS

- Animals: Male Wistar rats (12 weeks old)
- Protocol: 4 groups (n=7-8);
  rHuEPO doses (100, 200, 600 UI/kg/week body weight);
  control group with the vehicle (saline 0.9%);
  three times a week, by subcutaneous injections, during 3 weeks.
- Measurements (at starting and/or at the end of the protocol):
  renal function and hematological data (blood and urine samples);
  blood pressure and heart rate (tail cuff method);
  histological (Periodic acid-Schiff –PAS-stain) and qPCR studies
- Statistical analysis:
  ANOVA and post-hoc test Tukey (SPSS version 21.0);
  $p<0.05$ was considered as significant.

RESULTS

Table 1 – Hematological, biochemical and arterial pressure data at final time

	Control	rhEPO100	rhEPO200	rhEPO600
HEMATOLOGICAL DATA				
RBC (x 10^6/L)	7.99±0.17	8.20±0.13	9.41±0.12ab	10.53±0.39abc
Hemoglobin (g/L)	14.47±0.19	14.74±0.30	17.06±0.32ab	19.60±0.60abc
Hematocrit (%)	43.57±0.85	44.89±1.19	53.21±1.16ab	66.56±1.03abc
Reticulocytes (%)	2.33±0.18	2.63±0.31	1.90±0.27	4.17±0.51abc
Reticulocytes (x10^9/L)	205.68±16.16	215.01±26.67	179.34±26.07	535.60±52.38abc
BIOCHEMICAL DATA				
Urea (mg/dL)	21.02±0.33	22.36±0.51	21.70±0.42	23.06±0.70a
Creatinine (mg/dL)	0.37±0.02	0.32±0.02	0.36±0.03	0.40±0.02
Uric acid (mg/dL)	0.81±0.06	0.85±0.03	0.93±0.11	1.14±0.19
URINE 24H				
Urea (mg/dL)	5280.00±617.13	5950.00±575.39	6525.00±359.94	5400.00±733.03
Creatinine (mg/dL)	83.00±7.16	82.86±5.65	97.50±7.96	90.00±15.92
Uric acid (mg/dL)	10.58±0.66	8.43±0.97	11.00±1.47	11.88±1.01
Microalbuminuria (mg/L)	3.00±0.33	3.00±0.65	2.00±0.31	2.17±0.48
GFR (mL/h/rat)	108.76±5.27	111.11±6.21	109.34±6.87	110.88±16.21
ARTERIAL BLOOD PRESSURE DATA				
HR (Beat/min)	327.36±3.55	373.42±4.34a	354.37±2.41ab	338.07±1.19bc
SBP (mmHg)	105.20±0.90	119.06±1.12a	129.15±0.85ab	145.64±1.23abc
DBP (mmHg)	88.38±1.74	104.05±0.92a	100.73±1.30a	110.43±1.55ac
MBP (mmHg)	89.50±2.31	107.50±0.95a	107.31±1.71a	122.71±1.55abc

Results are presented as Mean ± Standard Error Mean; RBC – Red blood cells; GFR – Glomerular filtration rate; HR – Hear rate, SBP – Systolic blood pressure; DBP – Diastolic blood pressure; MBP – Mean blood pressure;
a) $p<0.05$ vs control group; b) $p<0.05$ vs rhEPO100UI; c) $p<0.05$ vs rhEPO 200UI

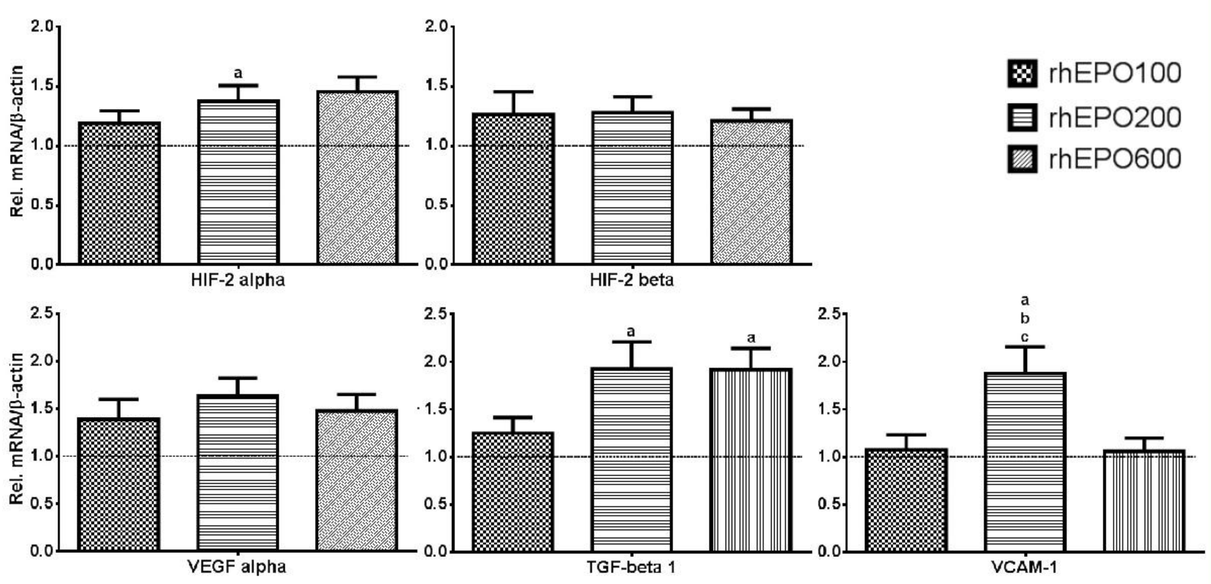

Figure 1 - Kidney gene expression (qPCR).
Results are presented as Mean Standard Error Mean

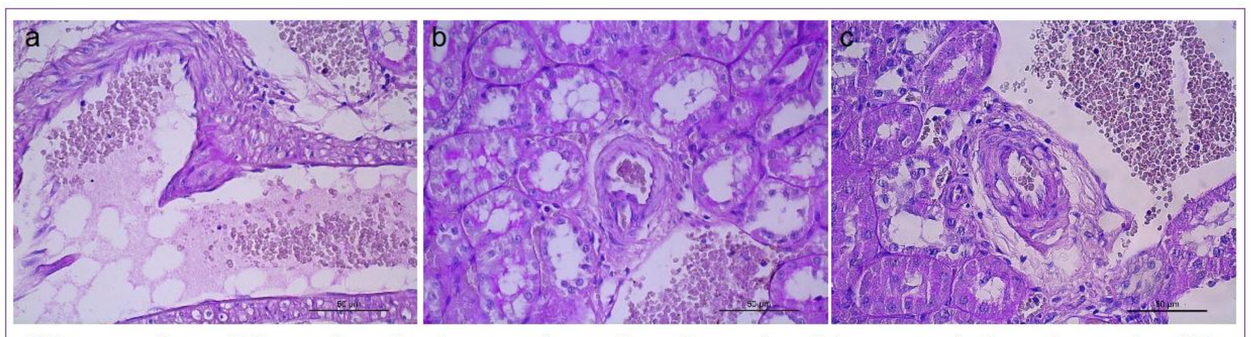

Figure 2 – Vascular lesions. Arteriosclerosis (a), arteriolosclerosis (b), arteriolar vacuolization (c), found in the rats from the 200 and 600 rhEPO doses groups (PAS).

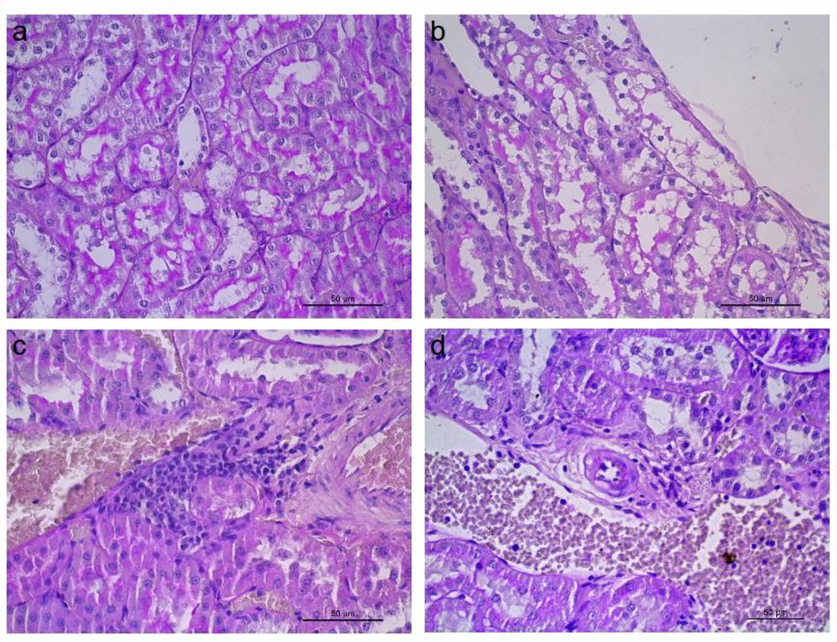

Figure 3 – Tubular lesions. Hidropic (a) and vacuolar (b) degeneration . Focus of interstitial inflammation (c) and tubular atrophy (IFTA) (d), found in the rats from the 200 and 600 rhEPO doses groups (PAS).

CONCLUSIONS

rHuEpo-induced hypertension did not impair renal function, as showed by the traditional blood and urinary markers of renal function; however, histological and genetic expression studies suggested that there is already kidney damage. Hypertension, by increasing the tone of renal blood vessels, compromises blood flow, leading to renal hypoxia, which activates the HIF pathway (observed in the 200rHuEPO group), to face hypoxic damage; nevertheless, the increase in TGF-beta 1 and VCAM-1 suggest kidney damage. Using a higher rHuEPO dose (600rHuEPO), the higher hematocrit, probably, blunts the HIF pathway activation, explaining the enhancement of cellular damage. In conclusion, rHuEpo-induced hypertension alters vascular and metabolic kidney pathways that will lead to early renal injury, even before significant changes in the traditional blood and urinary biomarkers of renal function are observed.

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