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Effect of Recombinant Human Erythropoietin (r-Hu EPO) Therapy on Blood Pressure in Dialysis Patients

Wpływ leczenia rekombinowaną erytropoetyną na ciśnienie krwi u chorych dializowanych

Recombinant human erythropoietin (r-Hu EPO) has been shown to benefit not only patients on hemodialysis (9, 24) but also those on continuous ambulatory peritoneal dialysis (15, 21) and intermittent peritoneal dialysis (13). The most important complication of r-Hu EPO therapy has been the increase in systemic blood pressure. Data from uncontrolled multicenter trials show a 35-45% incidence of development and 30-45% incidence of aggravation of hypertension when anemia is corrected by erythropoietin (8, 9, 22, 5).

Experimental studies made in our unit confirm these results and an increase in systolic and diastolic blood pressure was observed in hemodialysis and peritoneal dialysis patients treated with r-Hu EPO. (Fig. 1, 2).

Encephalopathy or grand-mal were sometime observed by many authors and were correlated with the increase in blood pressure during r-Hu EPO therapy (Table 1).

The increased blood pressure in patients treated with r-Hu EPO is caused by the correction of anemia rather than any direct effect of the medicine (18). Studies considering r-Hu EPO a direct vasoconstrictor have yielded inconclusive

Table 1. Incident complication during r-Hu EPO therapy in dialysis patients

Study		n	Hypertensive complication	
Winearls	1986	10	Encephalopathy	1
Eschbach	1987	18	Grand-mal	1
Casati	1987	14	Encephalopathy	1
Eschbach	1988	247	Grand-mal	2
Książek	1990	42	Encephalopathy	1
			Grand-mal	1

results but most of the evidence suggests that in conventional doses r-Hu EPO does not act as a direct vasoconstrictor (3, 10, 18).

Various mechanisms try to elucidate the effect of r-Hu EPO therapy on blood pressure as following: loss of hypoxic vasodilatation, increased blood viscosity, hemodynamic and volume changes, peripheral resistance, vascular responsiveness to vasopressor substance.

Verbeelen et al. (23) have observed decrease blood levels of 6-keto-1-α — prostaglandin comparing pre-and post- r-Hu EPO treatment.

But there appears to be general agreement that the predominant mechanism resulting in rise in blood pressure among subjects receiving r-Hu EPO is an increase in peripheral arterial resistance (1, 2, 16, 19). This rise in peripheral resistance may contribute to the evaluation of hypertension at least in a subset patients. However, Akiba et al. (1) has shown that changes of systemic vascular resistance during r-Hu EPO therapy did not correlate with changes in the mean blood pressure, but another author does not confirm these results (2, 19).

The increase in peripheral vascular resistance is a result of increase of hematocrit and rise of whole blood viscosity in patients treated with r-Hu EPO. Recently Schäefer et al. (19) have noted that plasma viscosity was enhanced in uremic subjects due to elevated fibrinogen levels prior to the onset of the study and remained unchanged during r-Hu EPO therapy. Thus, it is conceivable that the combination of high plasma viscosity with rising hematocrit values causes an excessive increase in whole blood viscosity.

Mayer et al. (16) observed rising whole blood viscosity during correction of anemia. This rise was connected with increased blood pressure.

Hemodynamic and volumen change are factors which could be considered as effects of r-Hu EPO on blood pressure (11). Chronic stable anemia in patients with end-stage renal disease is associated with an increased cardiac output and normal or lower peripheral vascular resistance (4, 17). A significant portion of the patients population is hypertensive, but correction of anemia with r-Hu EPO is very often associated with rise in arterial blood pressure.

Deschodt et al. (7) have showed increase of total peripheral resistance and decrease of cardiac output during correction of anemia and found a small but significant increase in mean arterial blood pressure. Although qualitative cardiac output and total peripheral resistance behave as in nonuremic anemic patients, the quantity of change of one or both of those parameters has to be inadequate in many uremic patients in view of the high incidence of hypertension accompanying r-Hu EPO treatment.

Schäefer et al. (20) have observed improved blood pressure in hypertensive patients when dry weight was decreased. The authors concluded that hypertension during r-Hu EPO therapy is dependent on inadequate body volume balance. Vascular responsiveness to vasopressor substance is antoher factor which could be considered in pathogenesis of hypertension during r-Hu EPO therapy.

Jadebait K. et al. (12) presented data of the effect of r-Hu EPO on renin and aldosterone concentration. During 3 months of r-Hu EPO treatment mean arterial blood pressure increased slightly from 85 to 95 mmHg but aldosteron concentration declined throughout the study and was lower than baseline.

Plasma renin activity and ANP concentration did not produce any significant change.

Different observations have been done by Cozma (6) who has observed increased serum aldosterone concentration, plasma renin activity and serum ANP concentration and blood pressure in r-Hu EPO treated dialysis patients. Changes in the renin-angiotensin-aldosterone system may contribute to the hypertension associated with r-Hu EPO administration.

Renina-angiotensin-aldosteron system is directly correlated with adrenergic system activity. Some authors have observed disturbance in adrenergic vascular reactivity in patients treated with r-Hu EPO.

Książek et al. (14) presented improved adrenergic activity in cold pressor test in patients treated with r-Hu EPO. The observed increased level of noadrenalin correlated with increased blood pressure.

In conclusion, hypertension is one of the most important complications during r-Hu EPO therapy. In the first week of treatment special care and frequent blood pressure measurments should be done. Remarkable target hematocrit, that is 30-35%, should be obtained slowly during 3-6 weeks. Early antihypertensive therapy prevents hypertensive complication.

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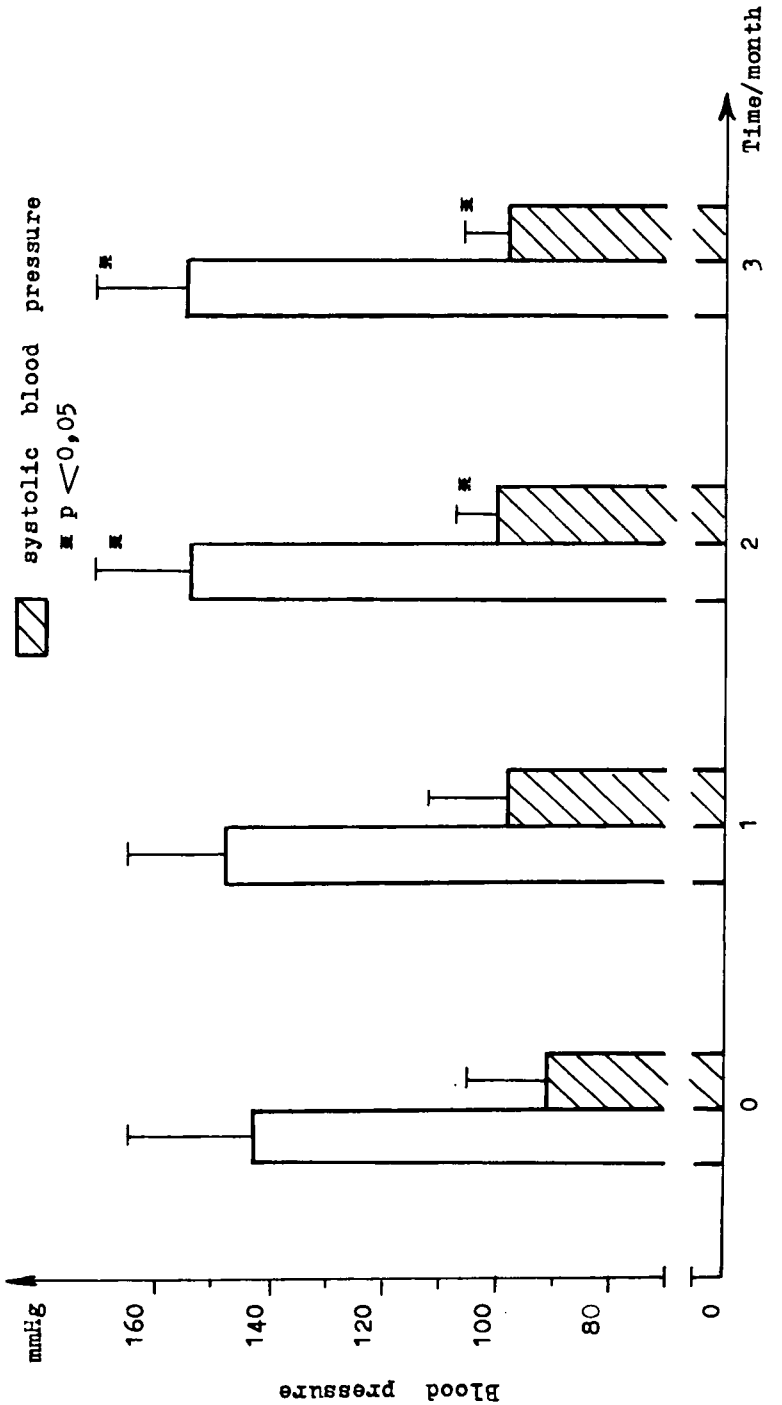

Fig. 1. Changes in blood pressure in ten patients on hemodialysis with r-Hu EPO therapy

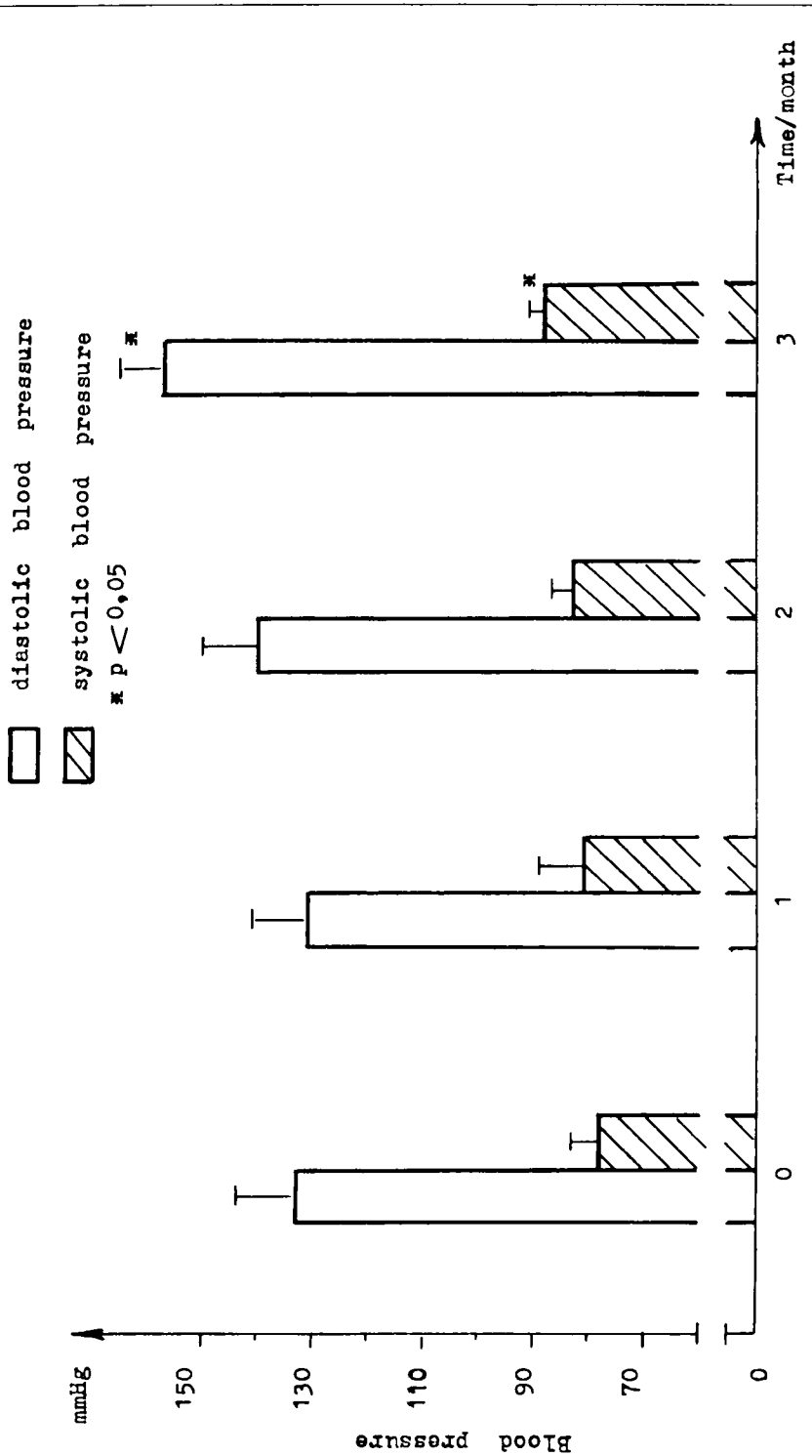

Fig. 2. Changes in blood pressure in fourteen patients on Intermittent Peritoneal Dialisis with r-Hu EPO therapy