HEMODYNAMIC MECHANISM OF THE ELEVATION IN BLOOD PRESSURE FOLLOWING THE IMPROVEMENT OF ANEMIA WITH RECOMBINANT HUMAN ERYTHROPOIETIN

KOJU KAMATA, M.D.¹, FUMIAKI MARUMO, M.D.²
AND KAORU ONOYAMA, M.D.³

Following the administration of recombinant human erythropoietin (rHuEPO) to 18 patients undergoing hemodialysis, the hematocrit (Ht) increased from 19.7 ± 1.8 to $31.0 \pm 2.0\%$. The incidence of hypertension according to the criteria of WHO was 11.1%. The systolic blood pressure (SBP) increased significantly from 120 ± 21 to 129 ± 26 mmHg ($p < 0.01$) and diastolic blood pressure (DBP) increased from 67 ± 14 to 73 ± 12 mmHg ($p < 0.05$). The cardiac index (CI) decreased significantly from 4.07 ± 1.13 to 3.56 ± 0.88 L/min/m² ($p < 0.05$). Total peripheral resistance index (TPRI) and blood volume (BV) increased significantly from $1,725 \pm 406$ to $2,170 \pm 643$ dynes/sec/cm⁻⁵/m² ($p < 0.001$) and from 78.9 ± 11.2 to 87.8 ± 14.8 ml/kg ($p < 0.005$) respectively. Pulse rate (PR) decreased significantly from 73.0 ± 10.7 to 65.9 ± 7.8 beats/min ($p < 0.01$). Patients who developed a blood pressure (BP) elevation of 10% or more for the mean blood pressure (MBP) showed a slight and insignificant decrease in CI from 3.65 ± 1.12 to 3.49 ± 1.06 L/min/m², which clearly contrasted to that in another group of patients who showed a reduced increase in MBP and a significant reduction in CI from 4.50 ± 1.03 to 3.63 ± 0.72 L/min/m² ($p < 0.05$). Stroke volume index (SVI) was unchanged in both groups but PR decrease significantly in the latter group. A significant increase in TPRI or BV was observed equally in both groups. The change in MBP significantly correlated with that in CI in all cases ($r = 0.64$, $p < 0.01$). The present study indicates that the correction of anemia with rHuEPO is associated with an increase in TPRI in all cases in chronic hemodialysis patients and BP elevation is regulated by the change in CI.

A notable improvement of anemia in chronic dialysis patients by the administration of recombinant human erythropoietin (rHuEPO) has been reported by

Key words:

Erythropoietin
Hypertension
Hemodynamics
Echocardiography
Chronic renal failure

many investigators!¹⁻⁴ In addition to the beneficial effects of rHuEPO treatment, some side effects, such as hypertension, hyperkalemia and obstruction of arterio-venous fistula have also been observed in these patients. Of these, hypertension has frequently been observed²⁻⁶ and has led to hypertensive encephalopathy and grand mal seizures!^{1-3,6-8} Although the correction of

(Received June 4, 1990; accepted December 12, 1990)

1. Department of Internal Medicine, Kitasato University School of Medicine, Kanagawa, Japan

2. Second Department of Internal Medicine School of Medicine, Tokyo medical and Dental University, Tokyo, Japan

3. Second Department of Internal Medicine Faculty of Medicine, Kyushu University, Fukuoka, Japan

Mailing address: Koju Kamata, M.D., Department of Internal Medicine, Kitasato University School of Medicine, 1-15-1 Kitasato, Sagami-hara, Kanagawa 228, Japan

anemia with rHuEPO in patients undergoing hemodialysis treatment has been reported to improve cardiac function^{9,10} the principal hemodynamic and volume changes, and the mechanism of blood pressure (BP) elevation, remain unknown. This study aimed to investigate the hemodynamic characteristics and the mechanism of blood pressure elevation during the improvement of anemia by rHuEPO.

PATIENTS AND METHOD

Patients

Eighteen severely anemic patients on maintenance hemodialysis with a hematocrit (Ht) of 23% or less and with functional class I of NYHA¹¹ participated in this study. They had received restricted sodium intake, less than 7g a day, and water intake, less than 500 ml a day, except water in meals. They were dialyzed in out-patient clinics 3 times a week and kept within weight limits of 2% before and after rHuEPO treatment. Patients receiving anti-hypertensive treatment or having cardio-vascular disorders, iron deficiency anemia, aluminum intoxication or amyloidosis were not included. Informed consent was obtained from each patient at the entry to this study.

Schedule of rHuEPO administration

rHuEPO (Kirin Brewery Co., Ltd., Tokyo) was administered intravenously 3 times a week at the end of each hemodialysis procedure, with doses of 1,500 IU in the initial 2 weeks, 3,000 IU during the next 4 weeks and 6,000 IU from the 6th week. Supplementary iron was given p.o. or i.v. if necessary. When the Ht exceeded 30% or a 10% increase was achieved, rHuEPO administration was discontinued.

Clinical and laboratory tests

BP was measured using a sphygmomanometer at the supine position after a 10 min rest. Blood samples were taken for complete blood cell counts and plasma levels of human atrial natriuretic peptide (hANP)¹² Blood volume (BV) was measured using ¹³¹I-HSA with a 10 min equilibrium and using a Volumetron (Ames Co., USA). All parameters were examined in the pre-dialysis state on the day or one day before hemo-

dialysis. The time of examination before and after rHuEPO treatment was kept the same for each patient.

Echocardiography

M-mode echocardiography was performed at the same time as blood sampling before and after rHuEPO treatment by the same examiner. Left ventricular end-systolic diameter (LVDS), end-diastolic diameter (LVDD), left atrial diameter (LAD), left ventricular end-diastolic volume (LVEDV), interventricular septum thickness (IVSTH), posterior wall thickness (PWTH), ejection fraction (EF) and stroke volume (SV) were obtained using methods previously reported!^{13,14} Stroke volume index (SVI) was calculated by dividing SV by the body surface area and cardiac index (CI) was obtained by multiplying SVI and PR. Total peripheral resistance index (TPRI) was calculated using the following formula:

$$\text{TPRI (dynes/sec/cm}^{-5}\text{/m}^2\text{)} = \frac{\text{mean BP (mmHg)}}{\text{CI (ml/min/m}^2\text{)}} \times 60 \times 1332$$

Criteria for an increase in BP

Though criteria for hypertension have been reported, a criterion for an increase or a decrease in BP has not. In this study, patients who had a 10% or more increase in mean BP after rHuEPO treatment constituted group-EV. The other patients constituted group-L.

Statistics

Wilcoxon's signed rank test was used for statistical analysis. All data are expressed as Mean $\pm$ SD.

RESULTS

Clinical data

Clinical data of the 18 patients (4 males and 14 females) with an average age of 41.5 ± 11.4 years old and an average duration of hemodialysis of 54.3 ± 35.9 months, are shown in Table I. Original disease consisted of 14 patients with chronic glomerulonephritis, 2 with polycystic kidney disease, one with rapidly progressive glomerulonephritis and one with chronic interstitial nephritis. Average systolic BP (SBP) and diastolic BP (DBP) before rHuEPO treatment were

TABLE I CLINICAL DATA BEFORE AND AFTER rHuEPO TREATMENT

Patient No.	Age Sex	Duration of HD (months)	Body weight (kg)*		Blood pressure (mmHg)		%change of MBP**	Group
			before	after	before	after		
1	21M	12	59.8	60.2	136/90	140/90	1.9	L
2	49M	106	43.0	43.3	110/70	114/70	2.4	L
3	52M	19	54.4	55.3	132/84	140/80	0	L
4	41F	50	45.7	45.5	108/70	120/80	12.0	EV
5	29F	104	46.5	46.9	110/70	108/74	2.4	L
6	33F	22	49.8	50.6	146/90	136/80	-9.2	L
7	53F	34	57.9	57.8	116/62	150/90	37.5	EV
8	67F	16	53.8	50.2	140/60	170/90	34.5	EV
9	42F	16	42.3	40.8	144/80	154/70	-3.0	L
10	42F	138	52.3	52.8	108/70	120/70	4.8	L
11	34F	56	46.5	46.3	90/56	88/52	-4.5	L
12	31M	34	49.7	50.1	138/42	137/65	20.3	EV
13	54F	58	55.2	55.7	72/43	83/53	18.9	EV
14	53M	28	62.5	62.1	144/60	153/61	4.5	L
15	37F	63	43.6	44.2	119/68	131/76	15.3	EV
16	25F	67	48.9	48.9	107/52	99/66	10.0	EV
17	42F	102	48.1	48.6	94/54	102/68	17.9	EV
18	42F	52	48.4	48.6	137/77	166/85	15.5	EV

*: Pre-dialysis body weight

**: Mean blood pressure

EV: Patients with an increase in MBP of 10% or more after rHuEPO treatment (Group-EV)

L: Patients with less than a 10% increase in MBP after rHuEPO treatment (Group-L)

TABLE II HEMATOLOGICAL DATA BEFORE AND AFTER rHuEPO TREATMENT

Patient No.	Duration of treatment (wks)	Hematocrit (%)		RBC ($\times 10^4/\text{mm}^3$)		Hemoglobin (g/dl)	
		before	after	before	after	before	after
1	13	18.7	30.9	240	333	7.5	9.9
2	13	19.6	31.0	208	322	6.5	10.7
3	12	16.4	33.2	179	357	5.5	10.3
4	14	18.1	28.9	188	327	5.3	9.3
5	12	18.7	26.0	197	312	5.9	8.9
6	11	20.9	30.0	237	332	6.7	9.2
7	17	18.2	32.3	182	305	6.2	9.5
8	18	18.6	32.8	179	321	5.6	10.1
9	11	21.6	32.8	282	362	7.4	10.1
10	11	21.0	32.0	225	326	6.8	10.1
11	10	22.5	33.5	238	364	6.7	9.4
12	7	21.5	30.0	217	316	6.8	9.9
13	11	22.0	29.5	253	328	6.4	8.6
14	11	21.0	33.0	215	337	6.5	9.7
15	10	20.5	31.5	215	335	6.6	10.4
16	9	20.0	28.0	213	320	6.4	9.8
17	11	18.5	31.0	189	326	5.9	10.0
18	9	17.0	31.0	184	294	5.6	9.3

120 $\pm$ 21 mmHg and 67 $\pm$ 14 mmHg respectively, and those after rHuEPO treatment were 129 $\pm$ 26 ($p<0.01$, $n=18$) and 73 $\pm$ 12 mmHg ($p<0.01$, $n=18$). The percentage change in mean BP (MBP) ranged between -9.2% and 37.5%. No patient had a change in mean BP between more than 5% and less than 10% in this study. Group-EV (G-EV) consisted of 9 patients whose MBP rose 10% or more and group-L (G-L) consisted of 9 patients whose MBP changed to a lower extent. Body weight (BW) was unchanged by rHuEPO treatment in all patients and also in the two subgroups.

Hematological data

Hematological parameters before and after rHuEPO treatment are listed in Table II. The average duration of rHuEPO treatment was 11.2 $\pm$ 2.6 weeks. Average Ht increased from 19.7 $\pm$ 1.8 to 31.0 $\pm$ 2.0% ($p<0.001$). In G-EV, Ht increased from 19.4 $\pm$ 1.7 to 30.6 $\pm$ 1.6% ($p<0.01$) and that in G-L increased from 20.0 $\pm$ 1.9 to 31.4 $\pm$ 2.4% ($p<0.01$). There were no significant differences between the groups.

Blood pressure

Systolic hypertension developed in 2 pa-

tients (No.8 and 18). The incidence of hypertension was 11.1%. SBP, DBP or MBP increased significantly in G-EV, but not in G-L. Pretreatment DBP was significantly lower in G-EV than in G-L ($p<0.05$, Table III).

Hemodynamic and volume parameters

Among all patients, echocardiographic parameters such as LVDD, LVDS, LVEDV, LAD, IVSTH and PWITH did not show significant changes following the rHuEPO treatment. TPRI values increased from 1725 $\pm$ 406 to 2170 $\pm$ 643 dynes/sec/cm⁻⁵/m² ($p<0.001$, $n=18$), and CI decreased from 4.07 $\pm$ 1.13 to 3.56 $\pm$ 0.88 L/min/m² ($p<0.05$, $n=18$). PR changed significantly from 73.0 $\pm$ 10.7 to 65.9 $\pm$ 7.8 beats/min ($p<0.01$, $n=18$), but SVI changed from 56.3 $\pm$ 15.5 to 54.4 $\pm$ 14.6 ml/m² (n.s., $n=18$). Although blood volume increased significantly from 78.9 $\pm$ 11.2 to 87.8 $\pm$ 14.6 ml/kg ($p<0.01$, $n=16$), hANP significantly decreased from 175 $\pm$ 98 to 117 $\pm$ 73 pg/ml ($p<0.01$, $n=13$). The cardiothoracic ratio (CTR) did not show a significant change.

Data in G-EV and G-L are shown in Table III. Parameters except DBP before rHuEPO treatment were not significantly

TABLE III HEMODYNAMIC AND VOLUME PARAMETERS BEFORE AND AFTER rHuEPO TREATMENT

	Group-EV (n=9)				Group-L (n=9)					
	before	(n)	after	(n)	p	before	(n)	after	(n)	p
Systolic BP (mmHg)	115±23	(9)	130±31	(9)	*	124±20	(9)	128±22	(9)	NS
Diastolic BP (mmHg)	59±12	(9) [#]	75±13	(9)	**	74±12	(9)	72±11	(9)	NS
Mean BP (mmHg)	77±13	(9)	93±18	(9)	**	91±14	(9)	91±13	(9)	NS
LVDD (mm)	50.1±4.5	(9)	49.9±4.8	(9)	NS	54.1±5.3	(9)	51.2±6.1	(9)	*
LVDS (mm)	33.2±6.5	(9)	32.2±7.6	(9)	NS	35.7±6.0	(9)	32.7±7.3	(9)	NS
LVEDV (ml)	120±25	(9)	119±27	(9)	NS	143±33	(9)	127±37	(9)	NS
LAD (mm)	34.0±3.4	(9)	34.5±4.5	(9)	NS	34.7±6.9	(9)	33.3±7.3	(9)	NS
LVSTH (mm)	10.12±2.48	(9)	9.36±1.59	(9)	NS	9.43±2.39	(9)	10.08±2.93	(9)	NS
PWTH (mm)	10.23±1.73	(9)	10.76±1.94	(9)	NS	9.67±2.24	(9)	11.14±1.85	(9)	NS
TPRI (dynes/sec/cm ⁻⁵ /m ²)	1792±494	(9)	2280±778	(9)	*	1658±307	(9)	2059±497	(9)	*
CI (L/min/m ²)	3.65±1.12	(9)	3.49±1.06	(9)	NS	4.50±1.03	(9)	3.63±0.72	(9)	*
SVI (ml/m ²)	51.3±15.7	(9)	52.5±15.9	(9)	NS	61.3±14.5	(9)	56.2±13.9	(9)	NS
PR (beats/min)	71.7±12.0	(9)	66.3±6.4	(9)	NS	74.3±9.6	(9)	65.6±9.3	(9)	*
Blood volume (ml/kg)	77.1±10.0	(9)	82.5±10.2	(7)	*	80.7±12.6	(9)	92.0±17.0	(9)	*
hANP (pg/ml)	150±52	(9)	100±79	(6)	NS	201±127	(9)	131±69	(7)	*
CTR (%)	49.3±5.3	(9)	49.1±5.0	(9)	NS	49.3±3.5	(9)	47.0±3.3	(9)	*

*: $p < 0.05$, **: $p < 0.01$ [#]: $p < 0.05$ vs before in Group-L

Group-EV: Patients with an increase in mean BP of 10% or more after rHuEPO treatment

Group-L: Patients with less than a 10% increase in mean BP after rHuEPO treatment

Fig. 1. Correlation between the change in MBP and that in CI following rHuEPO treatment.

- : Patient with a 10% or more increase in MBP (G-EV)
- : Patient with a lower increase in BP (G-L)

different between the two groups. LVDD in G-L decreased significantly ($p < 0.05$), LVEDV also decreased but the change was not statistically significant. Other parameters, such as LVDS, LAD, IVSTH and PWITH showed insignificant changes in either group. Although BP in G-EV increased significantly and that in G-L did not, TPRI increased significantly in both groups. The TPRI values did not differ between the two groups either before or after rHuEPO treatment. The reduction of CI was slight and insignificant in G-EV but was significant in G-L ($p < 0.05$). Similarly, PR significantly decreased in G-L ($p < 0.05$) but not in G-EV. SVI was unchanged either in G-EV or G-L. BV increased significantly in both groups. hANP and CTR decreased significantly in G-L, but not in G-EV. As shown in Fig. 1, the change in MBP significantly correlated with that in CI in all patients ($r = 0.64$, $p < 0.01$). There was no significant correlation between the change in MBP and that in TPRI ($r = -0.12$).

DISCUSSION

The incidence of hypertension induced by rHuEPO administration in chronic hemo-

dialysis patients has been reported to be 10%,¹ 13.3%⁶ or 22.2%². In this study, only two patients became hypertensive after rHuEPO treatment and the incidence of hypertension¹⁵ was calculated as 11.1%, but half the patients showed a 10% or more increase in MBP. BP seems to easily increase with rHuEPO treatment. There was a significant difference in pretreatment BP between G-EV and G-L. Patients in G-L who showed higher DBP before rHuEPO treatment, had relatively higher BV, LVDD, CI and hANP. It is therefore suggested that volume control in G-L may be relatively weak compared to that in G-EV. As shown by many investigators, uremic patients usually experience hyperdynamic circulation¹⁶⁻¹⁹ and the high CI correlates well with the expanded BV^{20,21}. A hyperdynamic state in chronic anemia was shown to be normalized by the correction of anemia by blood transfusion in a report by Neff et al¹⁶ where the elevated CI returned to a normal level at a Ht of 30% and an 80% increase in TPR was achieved at a Ht of 40%. As a possible mechanism of the TPR elevation, an increase in blood oxygen content which corrects hypoxic vasodilation²²⁻²⁴ and an increase in blood viscosity^{25,26} were indicated. In the present study, TPRI was elevated by the correction of anemia in all patients, in G-EV and even in G-L, where BP was not significantly changed. It is basically considered that rHuEPO administration could increase TPRI through the improvement of anemia in severely anemic hemodialysis patients. In association with a significant elevation in TPRI, CI decreased significantly in G-L and was unchanged in G-EV. Furthermore, there was a significant positive correlation between the change in MBP and that in CI. This may indicate that the change in CI in response to the improvement of anemia is responsible for the regulation of BP. Since a significant increase in BV was equally observed in both groups after rHuEPO treatment, CI seemed not to be directly regulated by BV. The significant reductions in CI, CTR, LVDD and hANP, irrespective of the BV increase, might have been induced by the redistribution of BV, that is, by the reduction of effective BV. On the other hand, reduction in LVDD, CTR and hANP in G-L may indicate the improvement of left ventricular

dilatation in patients with chronic renal failure.^{27,28} The significant reduction in PR after rHuEPO treatment reported by Nonnast-Daniel et al²² and Mayer et al²⁹ was also shown in G-L. This indicates that the chronotropic response is preserved well in G-L.

Acknowledgements

We are indebted to Dr. H. Otsuka, and Mr. J. Hashimoto of Kirin Brewery Co., Ltd. for data analysis and continued assistance. rHuEPO was provided by Kirin Brewery Co., Ltd., Tokyo, Japan.

REFERENCES

1. WINEARLES CG, OLIVER DO, PIPPAARD MJ, REID C, DOWNING MR, COTES PM: Effect of human erythropoietin derived from recombinant DNA on the anemia of patients maintained by chronic haemodialysis. *Lancet* 2: 1175, 1986
2. ESCHBACH JW, EGRIE JC, DOWNING MR, BROWNE JK, ADAMSON JW: Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. *N Engl J Med* 316: 73, 1987
3. CASATI S, PASSERINI P, CAMPISE MR, GRAZIANI G, CESANA B, PERISIC M, PONTICELLI C: Benefits and risks of protracted treatment with human recombinant erythropoietin in patients having haemodialysis. *Br Med J* 295: 1017, 1987
4. BOMMER J, ALEXIOU C, MÜLLER-BÜHL U, EIFERT J, RITZ E: Recombinant human erythropoietin therapy in haemodialysis patients: Dose determination and clinical experience. *Nephrol Dial Transplant* 2: 238, 1987
5. SAMTLEBEN W, BALDAMUS CA, BOMMER J, FASSBINDER W, NONNAST-DANIEL B, GURLAND HJ: Blood pressure changes during treatment with recombinant human erythropoietin. *Contr Nephrol* 66: 114, 1988
6. JACQUOT CH, FERRAGU-HAGUET M, LEFEBVRE A, BERTHELOT JM, PETERLONGO F, CASTAIGNE JP: Recombinant erythropoietin and blood pressure. *Lancet* 2: 1083, 1987
7. TOMSON CRV, VENNING MC, WARD MK: Blood pressure and erythropoietin. *Lancet* 1: 351, 1988
8. EDMUNDS ME, WALLS J: Blood pressure and erythropoietin. *Lancet* 1: 352, 1988
9. VERBEELEN D, BOSSUYT A, SMITZ J, HERMAN A, DRATWA M, JONCKHEER MH: Hemodynamics of patients with renal failure treated with recombinant human erythropoietin. *Clin Nephrol* 31: 6, 1989
10. LÖW I, GRÜTZMACHER P, BERGMANN M, SCHOEPPE W: Echocardiographic findings in patients on maintenance hemodialysis substituted with recombinant human erythropoietin. *Clin Nephrol* 31: 26, 1989
11. THE CRITERIA COMMITTEE OF THE NEW YORK HEART ASSOCIATION: Nomenclature and criteria for diagnosis of disease of the heart and vessels, 7th ed., Little Brown and Co., Boston, 1973
12. MARUMO F, SAKAMOTO H, ANDO K, ISHIGAMI T, KAWAKAMI M: A highly sensitive radioimmunoassay of atrial natriuretic peptide (ANP) in human plasma and urine. *Biochem Biophys Res Commun* 137: 231, 1986
13. TEICHHOLZ LE, KREULEN T, HERMAN MV, GORLIN R: Problems in echocardiographic volume determinations: Echocardiographic-angiographic correlations in the presence or absence of asynergy. *Am J Cardiol* 37: 7, 1976
14. SAHN DJ, DEMARIA A, KISSLO J, WEYMAN A: The committee on M-mode standardization of the American Society of Echocardiography: Recommendations regarding quantitation in M-mode echocardiography: Results of a survey of echocardiographic measurements. *Circulation* 58: 1072, 1978
15. WHO EXPERT COMMITTEE: Arterial hypertension. *WHO Technical Report Series* 628: 9, 1978
16. NEFF MS, KIM KE, PERSOFF M, ONESTI G, SWARTZ C: Hemodynamics of uremic anemia. *Circulation* 43: 876, 1971
17. KIM KE, ONESTI G, SCHWARTZ AB, CHINITZ JL: Hemodynamics of hypertension in chronic end-stage renal disease. *Circulation* 46: 456, 1972
18. GOSS JE, ALFREY AC, VOGEL JHK, HOLMES JH: Hemodynamic changes during hemodialysis. *Trans Am Soc Artif Intern Organs* 13: 68, 1967
19. MOSTERT JW, EVERS JL, HOBIKA GH, MOORE RH, KENNY GM, MURPHY GP: The haemodynamic response to chronic renal failure as studied in the azotaemic state. *Br J Anaesth* 42: 397, 1970
20. COLEMAN TG, BOWER JD, LANGFORD HG, GUYTON AC: Regulation of arterial pressure in the anephric state. *Circulation* 42: 509, 1970
21. KIM KE, ONESTI G, DELGUERCIO ET, GRECO J, FERNANDES M, EIDELSON B, SWARTZ C: Sequential hemodynamic changes in end-stage renal disease and the anephric state during volume expansion. *Hypertension* 2: 102, 1980
22. NONNAST-DANIEL B, CREUTZIG A, KÜHN K, BAHLMANN J, REIMERS E, BRUNKHORST R, CASPARY L, KOCH KM: Effect of treatment with recombinant human erythropoietin on peripheral hemodynamics and oxygenation. *Contr Nephrol* 66: 185, 1988
23. CROPP GJA: Hemodynamic responses to oxygen breathing in children with severe anemia. *Circulation* 40: 493, 1969
24. BARTLETT D, TENNEY SM: Tissue gas tensions in experimental anemia. *J Appl Physiol* 18(4): 734, 1963
25. MAYER G, STEFENELLI TH, CADA EM, THUM J, STUMMVOLL HK, GRAF H: Blood pressure and erythropoietin. *Lancet* 1: 351, 1988
26. DORMANDY JA: Clinical significance of blood viscosity. *Ann R Coll Surg Engl* 47: 211, 1970

27. COHEN MV, DIAZ P, SCHEUER J: Echocardiographic assessment of left ventricular function in patients with chronic uremia. *Clin Nephrol* **12**: 156, 1979
28. MIACH PJ, DAWBORN JK, LOUIS WJ, McDONALD IG: Left ventricular function in uremia: Echocardiographic assessment in patients on maintenance dialysis. *Clin Nephrol* **15**: 259, 1981
29. MAYER G, THUM J, CADA EM, STUMMVOLL HK, GRAF H: Working capacity is increased following recombinant human erythropoietin treatment. *Kidney Int* **34**: 525, 1988