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Effects of Hemoglobin Levels and Anti-hypertensive Therapy on Echocardiographic Parameters in Chronic Hemodialysis Patients

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Cardiovascular disease remains the major cause of death in hemodialysis (HD) patients. The aim of the present study was to examine if hemoglobin (Hb) levels and anti-hypertensive therapy are associated with changes in echocardiographic parameters in chronic HD patients. Sixty-seven (33 men and 34 women) HD patients were enrolled into this study. The echocardiographic studies were performed by an experienced senior cardiosonographer using an En Visor (Philips, Tokyo, Japan) ultrasound imager at baseline and follow-up. Because 10 g/dl was the median Hb, they were divided into a low Hb group with Hb less than 10 g/dl (n=32) and a high Hb group with Hb more than 10 g/dl (n=35). Anti-hypertensive agents including angiotensin receptor blockers (ARB) were largely underprescribed. The mean follow-up period was 2.7 ± 0.8 years. In high Hb group, the percentage of males and the use of ARB were significantly higher than in the low Hb group. Interventricular septum thickness (1.1 ± 0.2 vs 1.2 ± 0.2 cm, p=0.0082) and posterior wall thickness (1.0 ± 0.2 vs 1.2 ± 0.2 cm, p=0.0158) were significantly increased in the low Hb group, while there were no significant changes in echocardiographic parameters in the high Hb group. In addition, serum HDL-cholesterol levels and the percentage prescribed ARB were lower in the progression than in the regression group in left ventricular mass index. In conclusion, Hb levels and anti-hypertensive agents may modify cardiac remodeling in chronic HD patients.

Key words: cardiac hypertrophy, anemia, erythropoietin, angiotensin receptor blocker, hemodialysis

Introduction

Cardiovascular disease (CVD) remains the major cause of death in hemodialysis (HD) patients, with a mortality rate approximately 10 to 30 times greater than that of the general population[1]. The National Kidney Foundation (NKF) Task Force on CVD in Chronic Renal Disease issued a report emphasizing the high risk for CVD in patients with chronic kidney disease (CKD) and identified left ventricular hypertrophy (LVH) and coronary artery disease as the main targets for intervention[2]. Abnormalities in left ventricular size and function are common and may be have an incidence of 70-80% in dialysis patients as they start renal replacement therapy[3].

These alterations develop early in the course of renal disease, and their prevalence progresses in parallel with the decline in renal function[4]. Similar to the general population, LVH is a powerful predictor of mortality in dialysis patients[5][6], and its regression has been associated with a lower incidence of major cardiovascular events and a better survival rate[7][8]. Progression of LVH in CKD patients is multifactorial (pressure and volume overload, in addition to a number of emerging risk factors such as inflammation, hyperhomocysteinemia, high sympathetic nervous system activity and accumulation of the endogenous inhibitor of nitric oxide synthase asymmetrical dimethylarginine)[9], the principal etiologic factors being high left ventricular afterload and anemia[10][11].

The physiologic response to anemia has been well described and involves both hemodynamic and nonhemodynamic adaptations. Nonhemodynamic adaptations aimed at increasing tissue oxygen delivery include increases in red blood cell 2,3-diphosphoglycerate levels and increased erythropoietin synthesis to stimulate red blood cell production[12]. Hemodynamic changes include increased preload, decreased peripheral vascular resistance, and increased cardiac output[13]. The net result is an increased workload imposed on the left ventricle, contributing to the development of eccentric LVH. This response initially is adaptive; however, when sustained, it has adverse consequences on the myocardium. At the cellular level, myocytes experience an energy deficit, partly caused by ischemia, resulting in cell death. Cardiac fibroblasts proliferate, expanding the extracellular matrix of the myocardium, thereby causing myocardial fibrosis[14]. Therefore, it is likely that anemia correction using recombinant human erythropoietin (rHuEPO) may reduce the progression of LVH in HD patients. Recent studies also have shown that cardiac medications known for reducing cardiovascular risk are largely underprescribed in dialysis patients[15][16].

The aim of the present study was to longitudinally investigate whether hemoglobin levels (Hb) and anti-hypertensive therapy are associated with changes in LVH in chronic HD patients.

Patients and Methods

1. Study population

The study subjects were 67 maintenance HD patients (33 men and 34 women) treated at the Dialysis Unit of Koshin Clinic, Tokyo, Japan. HD was performed three times weekly (4 hours/day). The dialysis potassium concentration was 2.0 mEq/*l* and the calcium concentration was 3.0 mEq/*l*. Blood was drawn before starting each dialysis session. Hypertension was defined as systolic blood pressure $\geq$ 140 mmHg and/or diastolic blood pressure $\geq$ 90 mmHg, or use of antihypertensive medication. Diabetes mellitus (DM) was defined by World Health Organization (WHO) criteria[17]. Hyperlipidemia was defined as fasting serum total cholesterol $\geq$ 230 mg/dl, low density lipoprotein (LDL)-cholesterol $\geq$ 140 mg/dl, triglyceride $\geq$ 150 mg/dl, high density lipoprotein (HDL)-cholesterol $<$40 mg/dl or use of lipid-lowering medication. After enrollment, prescribed medications including angiotensin receptor blockers (ARB), angiotensin-converting enzyme inhibitors (ACEi), calcium channel blockers (CCB), and β-blockers according to the patients. All measurements, as listed below, were performed after each dialysis session. Each patient gave informed consent to participate in the study.

2. Cardiac ultrasonography

The echocardiographic studies were performed by an experienced senior cardiosonographer using an En Visor (Philips, Tokyo, Japan) ultrasound imager equipped with a 2.2/4.4 MHz (harmonics) phased-array 3S transducer, under continuous electrocardiographic recording at baseline and follow-up. The data were saved in the device's archive (digital archive, raw data) and the obtained images were recalled for calculation of the study parameters by the same interpreter, who was unaware of the patients' clinical status. The two-dimensional guided M-mode echocardiographic study was performed with a parasternal long-axis view, obtaining left ventricular end-systolic and end-diastolic dimensions, as well as interventricular septum and posterior wall thickness, all determined as the mean of five consecutive cardiac cycles, in accordance with the recommendations of the American Society of Echo-cardiography[18]. Left ventricular mass was measured using the formula of Deveraux {1.04 [(IVST + LVDd + PWT)^3 − LVDd^3] − 16.9; in which IVST is the interventricular septum thickness; LVDd, the left ventricular end-diastolic diameter; and PWT the posterior wall thickness} and was indexed for body surface area to estimate the left ventricular mass index (LVMI)[18][19]. Change in LVMI was obtained by subtracting the baseline LVMI value from the follow-up LVMI value. We chose to divide patients into the progression group, with an increase in changes in the LVMI, and the regression group, with a decrease in changes in the LVMI.

3. Biochemical analysis

Blood chemistry values were determined once a month. Whole blood was used for Hb and hema-

Table 1 Baseline characteristics in hemodialysis patients studied (n = 67)

	Unit	Value
Mean age	years	61.1 ± 11.1
Gender (%males)	%	49.3
Duration of HD	years	8.3 ± 5.6
Follow-up period	years	2.7 ± 0.8
Hemoglobin	g/dl	10.0 ± 0.6
Diabetes	%	40
Hypertension	%	79
Oral drugs (daily use)		
Use of ARB	%	43.3
Use of ACEI	%	13.4
Use of CCB	%	61.2
Use of β-blockers	%	1.5
Use of statins	%	10.5
Native arterioveous fistula	%	95.5
Arterioveous graft	%	4.5
Previous renal transplant	%	1.5
Underlying renal disease		
Diabetic nephropathy	%	37.3
Chronic glomerulonephritis	%	35.8
Nephrosclerosis	%	4.5
Polycystic kidney disease	%	6.0
Others	%	16.4
Cerebrovasucular disease	%	16.4
Peripheral artery disease	%	7.5
Cardiac complication	%	26.9
Cardiac valve disease	n	3
Coronary artery disease	n	3
Dilated cadiomyopathy	n	2
Arrhythmia	n	7
AAA	n	3

HD: hemodialysis, ARB: angiotensin receptor blocker, ACEi: angiotensin converting enzyme inhibitor, CCB: calcium channel blocker, AAA: abdominal aortic aneurysm.

tocrit; EDTA plasma, for fasting blood glucose and lipids, serum, for the other biochemical assays, including serum urea nitrogen (SUN), creatinine (Cr), albumin, calcium (Ca), phosphate (P), and C-reactive protein (CRP), all measured by automated methods. These parameters during the follow-up period are the means of at least 5 determinations. Kt/V is a unitless measure of dialysis adequacy in which K is the rate of urea clearance by dialysis, t is the time spent on dialysis, and V the patient's volume of urea distribution. Transferrin saturation (TSAT) and serum ferritin levels were monitored as indicators of ferrous status. Serum intact parathyroid hormone (intact PTH) was measured using a conventional radioimmunoassay and the means of 2 determinations were used during the follow-up period. Because 10 g/dl was the median Hb in our sample population, it was chosen as the cut-off value to divide patients into a low Hb group with Hb less than 10 g/dl (n= 32) and a high Hb group with Hb more than 10 g/dl (n=35). At entry, the prescribed weekly dose of rHuEPO was calculated.

4. Statistical analysis

All results are presented as means ± SD. For statistical comparison of means, the student t test for unpaired samples or, where applicable, the Mann-Whitney U-test, was used. ANOVA was used to compare serial changes over time between groups. Statistical analyses were performed using JMP version 5.1 software (SAS for Windows, Cary, NC, USA). P-values less than 0.05 were considered statistically significant.

Results

1. Baseline characteristics of HD patients at entry

Clinical parameters of HD patients in the present study are summarized in Table 1. The underlying diseases were type 2 DM in 37.3% of patients, chronic glomerulonephritis without DM in 35.8%, polycystic kidney disease in 6.0%, nephrosclerosis in 4.5%, and others in 16.4%. Their mean age was 61.1 ± 11.1 years, and the mean duration of dialysis was 8.3 ± 5.6 years. Thirty-three patients (49.3%) were men. Cardiac complications were present in 26.9%, cerebrovascular disease in 16.4% and peripheral artery disease in 7.5%. CCB, ARB, ACEi, and β-blockers were largely underprescribed. The mean follow-up period was 2.7 ± 0.8 years.

2. Baseline characteristics of HD patients divided into two groups according to Hb levels

In an effort to compare clinical variables between the low and high Hb groups at baseline, we assessed clinical characteristics including hemodynamic parameters, as summarized in Table 2. In the high Hb group, the percentage of males and ARB use were significantly higher than in the low Hb groups. There were no statistically significant differences, regardless of regression or progression, in any of other parameters between these two groups.

We also compared hematological parameters, as listed in Table 3, between the two groups. There

Table 2 Baseline characteristics of hemodialysis patients divided into two groups according to hemoglobin (Hb) levels

	Low Hb group	High Hb group	p-value
Number of patients	32	35	
Male/Female	11/21	24/11	0.016
Age (year)	61.2 ± 10.9	60.9 ± 11.3	n.s.
Duration of dialysis (years)	8.2 ± 5.5	8.5 ± 5.7	n.s.
Body mass index (kg/m^2)	21.1 ± 3.1	21.2 ± 2.2	n.s.
Hb (g/dl)	9.6 ± 0.4	10.5 ± 0.5	< 0.0001
Kt/V	1.4 ± 0.2	1.4 ± 0.3	n.s.
Systolic blood pressure (mmHg)	158.2 ± 24.3	151.0 ± 19.4	n.s.
Diastolic blood pressure (mmHg)	88.3 ± 12.1	86.0 ± 11.5	n.s.
Pulse pressure (mmHg)	71.8 ± 20.0	65.0 ± 12.2	n.s.
LVDd (cm)	4.8 ± 0.6	4.8 ± 0.7	n.s.
IVST (cm)	1.1 ± 0.2	1.2 ± 0.4	n.s.
PWT (cm)	1.0 ± 0.2	1.2 ± 0.2	n.s.
FS %	35.4 ± 7.8	33.9 ± 7.0	n.s.
LVMI (g/m^2)	151.7 ± 42.7	162.8 ± 56.5	n.s.
ARB (%)	10 (31.3)	20 (71.4)	0.010
ACEi (%)	5 (15.6)	4 (11.4)	n.s.
CCB (%)	18 (56.3)	23 (65.7)	n.s.
β-blocker (%)	1 (0.3)	2 (0.6)	n.s.

LVDd: left ventricular end-diastolic diameter, IVST: interventricular septum thickness, PWT: posterior wall thickness, FS: fractional shortening, LVMI: left ventricular mass index, ARB: angiotensin receptor blocker, ACEi: angiotensin converting enzyme inhibitor, CCB: calcium channel blocker.

Table 3 Baseline characteristics of hematological parameters in two groups according to hemoglobin (Hb) levels

	Low Hb group	High Hb group	p-value
Number	32	35	
Hb (g/dl)	9.6 ± 0.4	10.5 ± 0.5	< 0.0001
Hematocrit (%)	30.9 ± 1.4	33.0 ± 1.5	< 0.0001
Transferrin saturation (%)	23.1 ± 7.3	26.8 ± 8.4	n.s.
Ferritin (ng/ml)	109.4 ± 94.7	143.3 ± 204.5	n.s.
Albumin (g/dl)	4.1 ± 0.2	4.2 ± 0.3	n.s.
Kt/V	1.4 ± 0.2	1.4 ± 0.3	n.s.
C-reactive protein (mg/dl)	0.2 ± 0.4	0.2 ± 0.5	n.s.
Epoetin dose (IU/week)	5,835.9 ± 2,855.8	4,650.0 ± 2,519.2	n.s.

were no statistically significant differences in any of these parameters. Although the mean dose of rHuEPO tended to be higher (5,835.9 ± 2,855.8 IU/week) in the low Hb than in the high Hb group (4,650.0 ± 2,519.2 IU/week), these differences did not reach statistical significance.

3. Changes in hematological markers, hemodynamic variables and echocardiographic parameters in HD patients with low Hb levels

To examine the effects of low Hb levels on left ventricular function, we compared changes in echocardiographic parameters in addition to these in hematological markers and hemodynamic variables at baseline and follow-up. As shown in Table 4, there were no statistically significant differences in hematological markers including Hb, TSAT, ferritin and the weekly dose of rHuEPO, or in hemodynamic variables such as systolic and diastolic blood pressures, pulse pressure and Kt/V. Echocardiographic parameters including IVST (1.1 ± 0.2 vs 1.2 ± 0.2 cm, p=0.0082) and PWT (1.0 ± 0.2 vs 1.2 ± 0.2 cm, p=0.0158) were significantly increased at follow-up as compared with baseline. Although LVMI tended to be higher (160.0 ± 50.9 g/m^2) at follow-up than at

Table 4 Changes in hematological markers, hemodynamic variables and echocardiographic parameters in hemodialysis patients with low hemoglobin (Hb) levels

	Baseline	Follow-up	p-value
Number	32	32	
Hb (g/dl)	9.6 ± 0.4	10.3 ± 0.5	n.s.
Transferrin saturation (%)	23.1 ± 7.3	23.8 ± 6.2	n.s.
Ferritin (ng/ml)	109.4 ± 94.7	107.6 ± 79.7	n.s.
Epoetin dose (IU/week)	5,835.9 ± 2,855.8	4,781.3 ± 2,658.5	n.s.
Kt/V	1.4 ± 0.2	1.5 ± 0.2	n.s.
Systolic blood pressure (mmHg)	158.2 ± 24.3	153.5 ± 22.3	n.s.
Diastolic blood pressure (mmHg)	88.3 ± 12.1	86.1 ± 21.3	n.s.
Pulse pressure (mmHg)	71.8 ± 20.0	67.0 ± 17.6	n.s.
LVDd (cm)	4.8 ± 0.6	4.5 ± 0.6	0.0082
IVST (cm)	1.1 ± 0.2	1.2 ± 0.2	0.0158
PWT (cm)	1.0 ± 0.2	1.2 ± 0.2	0.0003
FS (%)	35.4 ± 7.8	34.5 ± 7.3	n.s.
LVMI (g/m^2)	151.7 ± 42.7	160.0 ± 50.9	n.s.

LVDd: left ventricular end-diastolic diameter, IVST: interventricular septum thichness, PWT: posterior wall thickness, FS: fractional shortening, LVMI: left ventricular mass index.

baseline (151.7 ± 42.7 g/m^2), the difference did not reach statistical significance. LVDd was significantly decreased at follow-up (4.5 ± 0.6 cm) versus baseline (4.8 ± 0.6 cm).

4. Changes in hematological markers, hemodynamic variables and echocardiographic results in HD patients with high Hb levels

To examine the effects of high Hb levels on left ventricular function, we compared changes in echocardiographic parameters in addition to hematological markers and hemodynamic variables at baseline and follow-up. As shown in Table 4, there were no statistically significant differences in hematological markers including Hb, TSAT, ferritin and the weekly dose of rHuEPO, or in hemodynamic variables such as systolic and diastolic blood pressures, pulse pressure and Kt/V. In addition, there were no statistically significant changes in echocardiographic parameters including LVDd, IVST, PWT, and LVMI.

5. Assessment of factors related to LVMI

The mean LVMI values at follow-up period were 160.0 ± 50.9 g/m^2 in the low Hb group and 171.8 ± 51.2 g/m^2 in the high Hb group. Changes in LVMI were evaluated by subtracting the baseline LVMI value from the follow-up LVMI value in all HD patients studied. The mean changes in LVMI were −38.7 ± 45.0 g/m^2 in the regression group (n=30) and 47.2 ± 39.1 g/m^2 in the progression group (n=37). Table 5 shows the comparisons of clinical parameters in HD patients with regression and progression of LVMI during follow-up period. Anti-hypertensive agents, as listed in Table 6, were used for at least 6 months during follow-up. Serum HDL-cholesterol levels and the percentage prescribed ARB were lower in the progression than the regression group.

Discussion

The present study showed IVST and PWT, but not LVMI, to be significantly increased during follow-up as compared with baseline in the low Hb group, while there were no statistically significant changes in other echocardiographic parameters. In addition, serum HDL-cholesterol levels and the percentage prescribed ARB were lower in the progression than the regression of LVMI group.

There has been only one randomized placebo-controlled study, conducted in 24 HD patients, showing moderate regression of LVMI (153-140 g/m^2 over 12 months) with ACEi use[20]. In a prospective observational study investigating the effect of antihypertensive medication on LVMI in 153 HD patients over a mean observation period of 54 months, London et al[21] reported moderate improvements in LVMI (174-162 g/m^2). Another randomized, but short-term, study conducted over 4 months in 146 HD patients failed to detect any re-

Table 5 Changes in hematological markers, hemodynamic variables and echocardiographic parameters in hemodialysis patients with low and high hemoglobin (Hb) levels

	Low Hb group			High Hb group		
	Baseline	Follow-up	p-value	Baseline	Follow-up	p-value
Number	32	32		35	35	
Hb (g/dl)	9.6 ± 0.4	10.3 ± 0.5	n.s.	10.5 ± 0.5	10.5 ± 0.7	n.s.
Transferrin saturation (%)	23.1 ± 7.3	23.8 ± 6.2	n.s.	23.1 ± 7.3	23.8 ± 6.2	n.s.
Ferritin (ng/ml)	109.4 ± 94.7	107.6 ± 79.7	n.s.	109.4 ± 94.7	107.6 ± 79.7	n.s.
Epoetin dose (IU/week)	5,835.9 ± 2,855.8	4,781.3 ± 2,658.5	n.s.	4,650.0 ± 2,519.2	4,478.6 ± 2,194.1	n.s.
Kt/V	1.4 ± 0.2	1.5 ± 0.2	n.s.	1.4 ± 0.3	1.4 ± 0.2	n.s.
Systolic blood pressure (mmHg)	158.2 ± 24.3	153.5 ± 22.3	n.s.	151.0 ± 19.4	148.9 ± 16.2	n.s.
Diastolic blood pressure (mmHg)	88.3 ± 12.1	86.1 ± 21.3	n.s.	86.0 ± 11.5	84.5 ± 10.7	n.s.
Pulse pressure (mmHg)	71.8 ± 20.0	67.0 ± 17.6	n.s.	65.0 ± 20.0	68.3 ± 12.2	n.s.
LVDd (cm)	4.8 ± 0.6	4.5 ± 0.6	0.0082	4.8 ± 0.7	4.7 ± 0.6	n.s.
IVST (cm)	1.1 ± 0.2	1.2 ± 0.2	0.0158	1.2 ± 0.4	1.3 ± 0.2	n.s.
PWT (cm)	1.0 ± 0.2	1.2 ± 0.2	0.0003	1.2 ± 0.2	1.2 ± 0.3	n.s.
FS (%)	35.4 ± 7.8	34.5 ± 7.3	n.s.	33.9 ± 7.0	33.7 ± 6.7	n.s.
LVMI (g/m^2)	151.7 ± 42.7	160.0 ± 50.9	n.s.	162.8 ± 56.5	171.8 ± 51.2	n.s.

LVDd: left ventricular end-diastolic diameter, IVST: interventricular septum thickness, PWT: posterior wall thickness, FS: fractional shortening, LVMI: left ventricular mass index.

Table 6 Comparison of clinical parameters in the hemodialysis patients with regression or progression of LVMI during follow-up period

	Regression	Progression	p-value
Number	30	37	
Age (years)	62.0 ± 9.8	60.3 ± 12.0	n.s.
Male gender (%)	13 (43.3)	21 (56.8)	n.s.
Duration of dialysis (years)	10.0 ± 7.0	7.0 ± 3.6	n.s.
Hb (g/dl)	10.3 ± 0.5	10.2 ± 0.4	n.s.
Epoetin dose (IU/week)	4,525.0 ± 2,195.3	5,239.9 ± 2,198.2	n.s.
Kt/V	1.5 ± 0.2	1.4 ± 0.2	n.s.
Systolic blood pressure (mmHg)	151.2 ± 22.0	154.5 ± 13.8	n.s.
Diastolic blood pressure (mmHg)	84.5 ± 13.2	8,535 ± 10.0	n.s.
Pulse pressure (mmHg)	64.1 ± 17.3	70.6 ± 10.6	n.s.
Calcium (mg/dl)	9.2 ± 0.6	9.2 ± 0.5	n.s.
Phosphorus (mg/dl)	5.4 ± 0.8	5.2 ± 0.6	n.s.
Intact PTH (pg/ml)	180.2 ± 76.4	160.0 ± 78.0	n.s.
Total cholesterol (mg/dl)	156.8 ± 28.1	157.2 ± 23.6	n.s.
HDL-cholesterol (mg/dl)	54.1 ± 16.1	47.0 ± 13.9	0.0421
Triglyceride (mg/dl)	96.6 ± 54.1	103.5 ± 58.3	n.s.
Albumin (g/dl)	4.1 ± 0.2	4.1 ± 0.3	n.s.
CRP (mg/dl)	0.3 ± 0.4	0.2 ± 0.2	n.s.
The use of ARB (%)	28 (93.3)	14 (37.8)	0.0831
The use of ACEi (%)	3 (10.0)	2 (5.4)	n.s.
The use of CCB (%)	17 (56.7)	30 (81.1)	n.s.
The use of β-blocker (%)	3 (10.0)	1 (2.7)	n.s.

HDL: high-density lipoprotein, CRP: C-reactive protein, ARB: angiotensin receptor blocker, ACEi: angiotensin-converting enzyme inhibitor, CCB: Calcium channel blocker, n.s.: not significant.

duction in LVMI when Hb was increased from a mean of 12.2 at baseline to 14 g/dl at study end[22]. However, since LVMI usually develops slowly, often over a period of years in most patients, regression or normalization cannot be expected to occur within such a short observation period.

The association between anemia and adverse cardiac outcomes in the dialysis population is well established. In a prospective cohort study by Harnett et al[23], 433 dialysis patients with a mean Hb level of 8.4 g/dl at the time of study initiation were followed-up for a mean of 41 months. LVH was present in 75% of subjects at initiation of renal replacement therapy. The investigators found that anemia was associated independently with the development of CHF and mortality. The relative risk for mortality was 1.18 per 1.0 g/dl decrease in the Hb level. In addition, LVH, similar to anemia, was an independent predictor of mortality. Subsequent studies in the HD population have confirmed that anemic patients are at increased risk of death, much of which is cardiac death. In a retrospective Medicare database study of more than 95,000 American HD patients, the relative risks of cardiac death were 1.40 and 1.18 for those with hematocrit levels of less than 27% and 27% to less than 30%, respectively, compared with a reference group with a hematocrit level of 30% to less than 33% after adjustment for baseline characteristics and comorbidities[24].

Observational evidence not only suggests that anemia is associated with adverse cardiac outcomes, but that treatment of anemia by rHuEPO replacement can lead to regression of LVH. In a prospective cohort study by Frank et al[25], the effect of normalization of Hb in HD patients, all of whom had LVH at baseline, was evaluated. Twenty-three subjects were treated with erythropoietin to achieve a target Hb of more than 12.5 g/dl for a mean of 8 months. Predialytic Hb increased from 10.5 g/dl at the time of study initiation to 13.4 g/dl. Hb normalization statistically significantly improved indices of left ventricular wall thickness and LVMI.

In the Canadian Normalization of Hemoglobin Study, 146 HD patients with concentric LVH or LV dilation were randomized to treatment with epoetin α to achieve a target Hb of 10 g/dl versus 13.5 g/dl. In patients with concentric LVH at baseline, there was no difference between treatment groups in the change in LVMI on echocardiography repeated at 40 weeks. Similarly, in subjects with LV dilation at baseline, there was no difference between treatment groups in the change in LV volume index at the end of the study. In short, normalization of Hb did not lead to regression of established LVH or dilation. The investigators suggested that the data were supportive of a potential role for a higher Hb target level in the prevention of LV dilation in those with established LVH, providing a rationale for further studies evaluating earlier intervention to prevent the development of structural cardiac disease[22].

The Canadian-European Normalization of Hemoglobin Study was a randomized, double-blind study of 596 HD patients without left ventricular dilation or symptoms of cardiac disease. Subjects were allocated randomly to a target predialysis Hb of 13.5 to 14.5 g/dl (mean Hb achieved, 13.3 g/dl at 24 weeks) or to partial correction of anemia with a target Hb of 9.5 to 11.5 g/dl (mean Hb achieved, 10.9 g/dl at 24 weeks) and serial echocardiograms were performed at 24, 48, and 96 weeks after study start. At the study conclusion, there was no difference in the primary outcome or change in LV volume index between treatment and control groups. In the lower target Hb group, the LV volume index increased by 8.3%, and it increased by 7.6% in the higher target group[26]. Thus, in this study, Hb normalization was not effective in preventing cardiac structural changes in HD patients. In addition, there was an excess of adverse events in the higher-level Hb group, specifically, the cerebrovascular event rate was increased.

It is well known that rHuEPO treatment leads to an increase in blood pressure and in the prevalence of hypertension. Hypertension is commonly treated with ACEi and/or ARB in patients with CKD. The use of ARB has been reported to decrease the responsiveness to rHuEPO in dialysis patients[27]. Therefore, it is suggested that the prescription rate of ARB in high Hb group is higher than those in low Hb group. Although previous studies have supported this hypothesis, some recent reports demonstrate that neither ACEi nor ARB clinically affect the progression of anemia[28][29]. Many factors including the study design, dose of antihypertensive agents, and different patient backgrounds could be

involved.

Our study has a few limitations. It was observational. This study presents findings from a consecutive series of patients treated following a prospective treatment regimen. Although observational studies have shown improvements in left ventricular geometry when Hb levels approach the normal range, these findings largely have gone unsupported in randomized trials of either partial correction or normalization of Hb in HD patients. This disparity highlights the importance of exercising caution in drawing causal conclusions from observational data. In particular, analyses based on observational data are susceptible to bias and residual confounding, which are both less likely in well-conducted, randomized, controlled studies.

In conclusion, our study showed that antihypertensive therapy using ARB, in combination with anemia correction, results in a slight reduction of LVH in chronic HD patients. Our results also suggest that a multifactorial approach to anemia correction, including cardioprotective therapy with ARB and strict control of hypertension, is necessary to achieve maximal effects aimed at complete regression of LVH to prevention of its development.

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慢性血液透析患者における心エコー所見に対するヘモグロビン濃度と降圧療法の効果

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維持透析患者において，心血管病変は主な死因のひとつである．我々は，ヘモグロビン(Hb)値と降圧療法が，慢性維持透析患者の心エコー所見の変化に影響するかどうか調べる縦断的研究を行った．対象は67名の維持透析患者（男性：33名，女性：34名）である．対象患者のHbの中央値が10 g/dlだったため，Hb10 g/dl未満（32名）の低値群と10 g/dl以上の（35名）の高値群に分けて検討した．アンジオテンシン変換酵素（ACE）阻害薬，アンジオテンシンII受容体拮抗薬(ARB)，カルシウム拮抗薬，β-遮断薬が広く使用されていた．平均観察期間は2.7±0.8年である．Hb高値群ではHb低値群と比べて，男性の比率とARB使用の割合が有意に高かった．また，Hb高値群では心エコーのパラメーターにおいて統計学的な有意差はなかったが，Hb低値群においては心室中隔厚（IVST；1.1±0.2 vs 1.2±0.2 cm，p=0.0082）と左室後壁厚（PWT；1.0±0.2 vs 1.2±0.2 cm，p=0.0158）は有意に増加していた．さらに，左室重量係数(LVMI)が抑制されている群に比し，増大している群では，血清の低比重リポプロテイン(HDL)-コレステロール値が有意に低値で，ARBの処方割合が少なかった．これらの結果から，慢性維持透析患者において，Hb値とARBによる降圧療法は，左室のリモデリングを修飾する可能性が示唆された．