Hemodynamic Changes by Recombinant Erythropoietin Therapy in Hemodialyzed Patients

Kiyotaka Satoh, Takashi Masuda, Yasuko Ikeda, Shingo Kurokawa, Kouju Kamata, Ryuichi Kikawada, Toshihiko Takamoto, and Fumiaki Marumo

Recombinant human erythropoietin therapy was given to 15 patients undergoing long-term hemodialysis with normal cardiac function. None of the patients had hypertension before the erythropoietin therapy and had received no antihypertensive agents. Before and after the erythropoietin therapy M-mode and pulsed Doppler echocardiographic studies, measurements of plasma volume by radioiodinated human serum albumin, and measurements of atrial natriuretic factor were carried out. After 6 weeks of erythropoietin therapy, hematocrit increased from 20.0 to 33.0%. Cardiac output, stroke volume, left ventricular diastolic dimensions, and left ventricular wall stress were all significantly decreased. Total peripheral resistance, interventricular septal thickness, and left ventricular posterior wall thickness were significantly increased. In Doppler echocardiographic studies, the mean velocity of aortic ejection flow and left ventricular acceleration time were decreased. The blood volume derived from plasma volume and hematocrit was not changed, whereas plasma atrial natriuretic factor concentration was significantly decreased. These data suggest that recombinant human erythropoietin administration suppressed the hyperdynamic cardiac state that was required to maintain oxygen delivery to the peripheral tissues in severe uremic anemia. (Hypertension 1990;15:262-266)

It is well-known that one of the main causes of death in patients undergoing long-term hemodialysis is cardiovascular involvement. Because they have severe anemia due to restricted production of erythropoietin at the kidney, these patients receive insufficient oxygen supply at the peripheral tissues, even with the increased cardiac output maintained. A hyperdynamic cardiac state also requires increased myocardial oxygen consumption because of increased cardiac work. Coronary artery disease is common in older patients undergoing hemodialysis, so that anemia may increase the chance of an ischemic event.

Recently, recombinant human erythropoietin (rHuEPO) has been available for use in patients undergoing dialysis. Nonnast-Daniel et al reported a significant increment of hematocrit from 21 to 33% within 10–12 weeks of rHuEPO administration. However, severe hypertension or hypertensive encephalopathy was noted in some cases and is a major complication of rHuEPO administration. In the present study, we attempted to clarify the clinical usefulness of rHuEPO therapy and to evaluate the hemodynamic changes that might affect cardiac function in patients undergoing long-term hemodialysis.

Methods

Fifteen patients undergoing long-term hemodialysis (11 women and four men), ranging from 24 to 77 years old (42±10 yr, mean±SD), were studied. They underwent dialysis 4–5 hours a day, three times a week with a hollow fiber dialyzer with 200 ml/min blood flow and 500 ml/min dialysate flow. Anemia was severe in all patients, with hematocrit lower than 23%, but none of the patients had hypertension or a history of congestive heart failure before the rHuEPO therapy. The 3,000 units of rHuEPO (supplied by Kirin Brewery Co. Ltd., Tokyo, Japan) was dissolved into 2 ml citrate buffer containing 0.25% human albumin, pH 6.4–7.4, and was infused from the venous line of the dialysis system just before the end of each hemodialysis session. The doses of rHuEPO were 30...
units/kg during the initial 2 weeks and 60 units/kg during the next 4 weeks, three times weekly. Blood cell counts were performed weekly. Before and at the end of the rHuEPO protocol, M-mode and pulsed Doppler echocardiography were carried out by the same specialized examiner. An ultrasonic system (77020AC, Hewlett Packard Co., Palo Alto, California) with a 2.5 MHz single element transducer was used. Heart rate and blood pressure were recorded at the same time. The measurements of interventricular septal thickness (IVST), left ventricular posterior wall thickness (LVPWT), left ventricular internal dimensions during systole (LVDs) and during diastole (LVDd) were made in three cardiac cycles, and the mean values were used. Left ventricular end-diastolic volume (LVEDV), ejection fraction, stroke volume, and cardiac output were obtained by the method of Teichholz et al.5 The Doppler-estimated aortic and pulmonic ejection flow velocities were adjusted according to the flow direction. And peak flow velocity, mean flow velocity, acceleration time, deceleration time, preejection period, and ejection time were measured as shown in Figure 1. Total peripheral resistance (TPR) was calculated by the following formula:

$$\text{TPR} = \frac{\text{mean BP} - 10 \text{ mm Hg}}{\text{CO}} \times 1332 \times 60 \text{ dyne-sec-cm}^{-5}$$

where BP is blood pressure and CO is cardiac output.

The left ventricular wall stress (LVWS) was calculated by the method of Reicheck et al6 as

$$\text{LVWS (g/cm}^2) = \frac{0.334 \times P_s \times \text{LVDs}}{\text{LVPWTs}(1 + \text{LVPWTs/LVDs})}$$

where $P_s$ is systolic blood pressure and LVPWTs is end-systolic left ventricular posterior wall thickness.

Plasma volume was measured by radioiodinated human serum albumin, and blood volume was derived from the equation as

$$\text{BV (ml/kg)} = \frac{\text{PV} \times 100}{100 - \text{Ht}}$$

where BV is blood volume, PV is plasma volume, and Ht is hematocrit. Plasma atrial natriuretic factor (ANF) concentration was estimated by a highly sensitive method of radioimmunoassay.7 Both reverse-phase, high-performance liquid chromatography (RP-HPLC) and gel permeation chromatography (GPC) were applied to determine the ANF molecular forms.7

Statistical analysis was performed by Wilcoxon's paired $t$ test.

Results

Blood cell counts and M-mode measurements are summarized in Table 1. After the administration of rHuEPO, hematocrit increased from 20.0±1.6% (mean±SD) to 33.0±1.9% ($p < 0.01$). Hemoglobin and red blood cells also significantly increased. Heart rate was changed from 71.8±11.4 to 67.2±11.1 beats/min but was not significant. The mean values of systolic and diastolic blood pressures were changed from 127.8±12.0 to 135.8±18.2 and from 72.0±10.3 to 79.6±12.4 mm Hg, respectively, but were not statistically significant. Among the studied patients, two showed elevated systolic and diastolic blood pressure as 126/70 (baseline) to 170/100 (after rHuEPO) and 144/80 to 168/96 mm Hg, and one showed only sys-
TABLE 1. Hemodynamic Changes After Recombinant Erythropoietin Administration

<table>
<thead>
<tr>
<th>Hemodynamic variables</th>
<th>Baseline</th>
<th>After rHuEPO</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>5,137±1,373</td>
<td>5,343±1,365</td>
<td>NS</td>
</tr>
<tr>
<td>RBC (×10⁶)</td>
<td>227±40</td>
<td>343±39</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>6.6±0.7</td>
<td>9.7±1.0</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Ht (%)</td>
<td>20.0±1.6</td>
<td>33.0±1.9</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>71.8±11.4</td>
<td>67.2±11.1</td>
<td>NS</td>
</tr>
<tr>
<td>BPs (mm Hg)</td>
<td>127.8±12.0</td>
<td>135.8±18.2</td>
<td>NS</td>
</tr>
<tr>
<td>BPd (mm Hg)</td>
<td>72.0±10.3</td>
<td>79.6±12.4</td>
<td>NS</td>
</tr>
<tr>
<td>IVST (7-12 mm)</td>
<td>7.8±1.2</td>
<td>9.4±2.1</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>LVPWT (7-11 mm)</td>
<td>8.2±1.4</td>
<td>10.2±1.7</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>LVDD (37-55 mm)</td>
<td>51.7±4.7</td>
<td>48.6±3.8</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>LVDs (26-35 mm)</td>
<td>31.2±4.8</td>
<td>28.6±4.4</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDV (80-180 ml)</td>
<td>129.0±27.5</td>
<td>111.3±20.8</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>EF (53-80%)</td>
<td>70±7</td>
<td>71±8</td>
<td>NS</td>
</tr>
<tr>
<td>SV (35-103 ml)</td>
<td>89.1±16.6</td>
<td>79.2±16.0</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>CO (2.6-7.2 l/min)</td>
<td>6.2±1.6</td>
<td>5.3±1.2</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>TPR (700-1,600 dynes-sec-cm⁻²)</td>
<td>1,106±258</td>
<td>1,378±324</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Wall stress (g/cm²)</td>
<td>60.9±16.9</td>
<td>49.1±19.7</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Ao Peak V (80-130 cm/s)</td>
<td>101±21</td>
<td>102±21</td>
<td>NS</td>
</tr>
<tr>
<td>Ao Mean V (60-90 cm/s)</td>
<td>76±12</td>
<td>63±13</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Ao ACT (msec)</td>
<td>95.2±17.2</td>
<td>87.6±10.5</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Ao DCT (msec)</td>
<td>187.7±28.6</td>
<td>193.7±53.6</td>
<td>NS</td>
</tr>
<tr>
<td>Ao PEP/ET</td>
<td>0.33±0.06</td>
<td>0.37±0.10</td>
<td>NS</td>
</tr>
<tr>
<td>Blood volume (60-90 ml/kg)</td>
<td>73.1±9.6</td>
<td>75.6±12.1</td>
<td>NS</td>
</tr>
<tr>
<td>ANF (36-80 pg/ml)</td>
<td>121.0±82.7</td>
<td>85.4±63.5</td>
<td>p&lt;0.01</td>
</tr>
</tbody>
</table>

Values are mean±SD. rHuEPO, recombinant human erythropoietin; WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; Ht, hematocrit; HR, heart rate; BPs, systolic blood pressure; BPd, diastolic blood pressure; IVST, interventricular septal thickness; LVPWT, left ventricular posterior wall thickness; LVDD, left ventricular diastolic dimensions; LVDs, left ventricular systolic dimensions; LVEDV, left ventricular end-diastolic volume; EF, ejection fraction; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance; Ao peak V, aortic ejection peak flow velocity; ACT, acceleration time; DCT, deceleration time; PEP, pre-ejection time; ET, ejection time; ANF, atrial natriuretic factor.

tolic elevation from 132/78 to 156/80 mm Hg. None of the patients had any neurological symptoms.

In the measurements of M-mode echocardiography, IVST and LVPWT were increased (p<0.01), whereas LVDd decreased (p<0.01). LVEDV was decreased from 129.0 to 111.3 ml (p<0.05), but ejection fraction was not changed. Stroke volume and cardiac output were decreased from 89.1 to 79.2 ml (p<0.05) and 6.2 to 5.3 l/min (p<0.05), respectively. TPR significantly increased from 1,106 to 1,373 dynes-sec-cm⁻², and systolic left ventricular wall stress decreased from 60.9 to 49.1 g/cm².

In the Doppler study, mean aortic ejection flow velocity and aortic acceleration time were both significantly decreased (p<0.05) as shown in Figure 2. However, acceleration or deceleration time of the mitral and tricuspid filling profiles were not significantly changed. Blood volume did not change significantly with the administration of rHuEPO (from 73.1±9.6 to 75.6±12.1 ml/kg), whereas plasma ANF concentration was significantly decreased from 121.0±82.7 to 85.4±63.5 pg/ml as shown in Figure 3. The plasma ANF molecular forms obtained from GPC and RP-HPLC at baseline (before rHuEPO) and after treatment in a patient undergoing hemodi-

Discussion

Severe anemia is one of the risk factors for the life span of patients undergoing hemodialysis. Recently, rHuEPO has come into clinical use to restore the severe anemia in those patients. The effects of rHuEPO on cardiac hemodynamics have not yet been clarified; however, some reports have indicated abrupt onset of hypertension. The major hemodynamic response induced by severe anemia is a hyperdynamic cardiac output state to maintain a sufficient oxygen supply to the peripheral tissues. Less than 25% of hematocrit is considered to be the critical level of renal anemia inducing hyperdynamic cardiac function. The dilatation or the collapse of capillary beds may be induced secondary to hypoxia and that makes an afterload reduction (decreased wall resistance). The blood perfusion to the peripheral tissue may be increased by both afterload reduction and hyperdynamic cardiac state as a compensatory mechanism.
In the present study, the rHuEPO therapy restored the severe uremic anemia. Subsequently, LVEDV, stroke volume, and cardiac output were all decreased. The significant decrease in heart size led to the increase of IVST and LVPWT with the reduction of LVWS. However, the ejection fraction was not changed significantly. The mean values of systolic and diastolic blood pressures in studied patients either had no change or were mildly elevated. Three patients showed elevated systolic and diastolic blood pressures without symptoms. We designed the initial administration of rHuEPO as a relatively small dose, and no blood pressure elevation was observed in this period. The evidence of hypertension may relate to the doses and the trial duration. The previously reported cases of hypertensive encephalopathy were evident in trials with more than 100 units/kg. Improved oxygen delivery in the recovery from anemia might cause the increment of vascular tonus, and blood viscosity is increased with the associated elevation of hematocrit. Both increased blood viscosity and vasoconstrictive effects might cause the increment of vascular resistance at the peripheral vessels. The escape from the hyperdynamic state with reduced cardiac output and slight elevation of systemic blood pressure, usually caused by administration of the rHuEPO, caused the increment of TPR.

It is known that the serum concentration of ANF is increased by atrial volume expansion or mechanical wall stretching. Blood volume before and after the rHuEPO therapy was not changed significantly; however, the preload reduction (reduced LVEDV) and stabilization of the hyperdynamic cardiac state might be the reasons for decreased ANF. The mean velocity of aortic ejection flow was significantly decreased in association with decreased cardiac output. However, increased blood viscosity did not cause the increment of peak acceleration velocity of aortic ejection flow.

In the present study, we selected patients with normal cardiac function (New York Heart Association functional class I) so that none of the patients had evidence of heart failure. Different hemodynamic alterations secondary to rHuEPO therapy may appear when a clinical trial includes the high risk patients with hypertensive heart disease or ischemic heart disease. Although whether rHuEPO improves congestive heart failure is unknown, the analysis of molecular forms of ANF may give some idea in the
evaluation of cardiac dysfunction. We previously reported that $\beta$-ANF was only seen in chronic congestive heart failure, and it disappeared after successful therapy for heart failure. No evidence of $\beta$-ANF was observed in the present study.

The hemodynamic alterations caused by rHuEPO therapy were reduction of LVWS and cardiac output, increment of total peripheral resistance, and suppression of ANF secretion. Elevation of blood pressure, which was a possible side effect of rHuEPO therapy, was not obvious in the present study. We conclude that rHuEPO therapy benefits in restoration of red blood cells in severe uremic anemia as well as reduction of cardiac work with improvement of the oxygen supply to the peripheral tissues.

References


Key Words • erythropoietin • hemodialysis • echocardiography
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