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Treatment of orthostatic hypotension with erythropoietin

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TREATMENT OF ORTHOSTATIC HYPOTENSION WITH ERYTHROPOIETIN

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Abstract *Background and Methods.* Patients with orthostatic hypotension caused by autonomic neuropathy frequently have a decreased red-cell mass. This would be expected to compromise their effective circulating blood volume and aggravate the orthostatic hypotension. We studied the effect of increasing the red-cell mass with erythropoietin, given subcutaneously in a dose of 50 U per kilogram of body weight three times a week for 6 to 10 weeks to eight patients with orthostatic hypotension — four men, one teenage boy, and three women (age range, 17 to 68 years). Four patients had type I diabetes mellitus and autonomic neuropathy, three patients had pure autonomic failure, and one patient had sympathotonic orthostatic hypotension. Seven patients received fludrocortisone (0.1 or 0.2 mg per day) before, during, and after the trial of erythropoietin. The red-cell volume, plasma volume, and hemodynamic response to orthostatic stress were measured before and after therapy.

Results. Erythropoietin increased the mean (±SD) hematocrit from 0.34±0.04 to 0.45±0.04 ($P<0.005$) and increased the red-cell volume from 16.8±3.9 to 25.3±3.1 ml per kilogram ($P<0.005$), but had no effect on plasma volume. The systolic blood pressure increased from 81±11 to 100±24 mm Hg ($P<0.01$) and the diastolic blood pressure increased from 46±10 to 63±18 mm Hg ($P<0.01$) while the patients were standing. The average systolic and diastolic blood pressure while the patients were supine did not increase significantly, although hypertension in the supine position developed in three patients. Orthostatic dizziness improved during treatment in six of the eight patients.

Conclusions. In patients with orthostatic hypotension, increasing the red-cell volume with erythropoietin elevates blood pressure while standing. Possible long-term adverse effects are not known. (N Engl J Med 1993;329: 611-5.)

ALTHOUGH the autonomic nervous system has a recognized role in the maintenance of sodium and water balance and the regulation of plasma volume, little is known about its role in the regulation of red-cell volume. This question is of interest because some patients with autonomic neuropathy are anemic and have a decreased red-cell mass.[1-3] A decreased red-cell mass would be expected to compromise effective circulating blood volume and therefore aggravate hypotension in these patients. To address this issue, we determined the effect of increasing the red-cell mass with erythropoietin on the hemodynamic response to orthostatic stress in eight patients with orthostatic hypotension.

METHODS

Patients

We studied eight patients with orthostatic hypotension (defined as a decrease in systolic blood pressure of more than 20 mm Hg and a decrease in diastolic blood pressure of more than 10 mm Hg during the first three minutes after the patients changed from the supine to the upright posture) and a documented deficit in red-cell mass. Four patients had type I diabetes mellitus and multiple features of diabetic autonomic neuropathy, including gastroparesis diabeticorum. Three patients had pure autonomic failure, and one patient had sympathotonic orthostatic hypotension (Table 1). Three patients had mild renal insufficiency, with serum creatinine concentrations between 1.4 and 1.6 mg per deciliter (124 to 142 μmol per liter). All the patients had a history of chronic orthostatic dizziness (from 8 months to 10 years in duration), and six had a history of orthostatic syncope. Seven patients were receiving fludrocortisone (Florinef, Bristol-Meyers Squibb, Evansville, Ind.) therapy when referred to us; Patient 8 had taken it in the past but discontinued it because of ankle edema. The fludrocortisone was continued in the seven patients at a daily dose of 0.1 mg (three patients) or 0.2 mg (four patients). Patients with reversible causes of orthostatic hypotension — Addison's disease, gastrointestinal bleeding, and dehydration — were excluded on the basis of history, physical examination, and appropriate laboratory tests, as were patients with hypertension that occurred when they were supine (a blood pressure of 150/100 mm Hg or greater) and patients with a history of congestive heart failure, seizures, liver disease, chronic renal failure, or thromboembolic events. The protocol was approved by the institutional review boards of Temple University, the State University of New York Health Sciences Center at Syracuse, and West Virginia University.

We assessed autonomic function by measuring the beat-to-beat variation with deep breathing,[4] the heart-rate response to the Valsalva maneuver,[4] the plasma norepinephrine response to orthostatic stress,[5-7] and autonomic surface potentials.[8] All assessments, except the plasma norepinephrine measurements, were performed at least twice, and the mean result was calculated.

The beat-to-beat variation with deep breathing was determined by measuring RR intervals electrocardiographically for 2 minutes while the patients breathed deeply according to a 10-second cycle of inspiration and expiration. The variation, calculated by subtracting the minimal heart rate from the maximal, is an index of respiration-induced sinus arrhythmia, which is mediated by the parasympathetic innervation of the heart.[4] The heart-rate response to the Valsalva maneuver was measured electrocardiographically while the patients blew for 15 seconds into a polyethylene tube connected to a manometer to generate a pressure of 40 mm Hg. The degree of post-Valsalva bradycardia was determined by calculating the Valsalva ratio — the longest RR interval after the maneuver divided by the shortest interval during the maneuver. This test assesses the integrity of cardiac innervation, the baroreceptor reflex, and the efferent limb of the sympathetic nervous system.[4] The plasma norepinephrine response to orthostatic stress also tests the efferent limb of the sympathetic nervous system. Autonomic surface potentials were measured from recording electrodes over the palms and soles.[8] The stimulating electrode was placed over the median nerve, and four stimuli of gradually increasing intensity were delivered. The electrodermal response is a measure of sympathetic sudomotor activity in the extremities. The test is useful in determining whether autonomic dysfunction is focal or diffuse.[9,10]

Measurement of the Hemodynamic Response to Orthostatic Stress

Blood pressure and heart rate were measured electronically with an Accutorr I Datascope (Paramus, N.J.) or a Dinamap Vital Signs Monitor (Critikon, Tampa, Fla.). All hemodynamic measurements

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Table 1. Clinical Characteristics of the Patients with Orthostatic Hypotension Who Received Erythropoietin.*

Patient No.	Age (yr)/ Sex	Diagnosis	Duration of Orthostatic Hypotension	Plasma Norepinephrine†		Beat-to-Beat Variation with Deep Breathing	Post-Valsalva Bradycardia: Tachycardia Ratio	Autonomic Surface Potentials
				supine	standing			
				pg/ml		beats/min		
1	42/M	Diabetic autonomic neuropathy	2 yr	149	379	3‡	1.06‡	Absent
2	39/M	Diabetic autonomic neuropathy	3 yr	127	189‡	3‡	1.16	Absent
3	48/M	Diabetic autonomic neuropathy	3 yr	119	157‡	4‡	1.33	Absent
4	58/F	Diabetic autonomic neuropathy	8 yr	44‡	57‡	0‡	1.00‡	ND
5	44/F	Pure autonomic failure	4 yr	331	662	29	1.24	ND
6	68/M	Pure autonomic failure	10 yr	242	505	ND	ND	ND
7	17/M	Sympathotonic orthostatic hypotension	8 mo	57‡	111‡	8‡	1.25	Absent
8	67/F	Pure autonomic failure	18 mo	167	199‡	3‡	1.16	Normal

*ND denotes not done.

†To convert values for plasma norepinephrine to picomoles per milliliter, multiply by 0.0059.

‡Value is below the normal range for age-matched normal subjects.

were made in the morning. The patients were instructed to rest quietly for at least five minutes before blood pressure was measured in the supine position and were then asked to stand for five minutes to assess the orthostatic change in blood pressure. In two patients who were unable to stand for five minutes, the blood pressure was measured after two minutes of standing. The results presented generally represent the mean of hemodynamic measurements made on two or three days.

Evaluation of Anemia

The nature of anemia was evaluated by measuring the red-cell indexes and serum iron-binding capacity, serum iron concentrations, and in some patients, serum erythropoietin, ferritin, folic acid, and vitamin B_{12} concentrations. Serum ferritin was measured by an immunoradiometric assay, folic acid and vitamin B_{12} were measured by radioimmunoassays, and erythropoietin was measured by a double-antibody immunoassay.[11]

Study Protocol

Erythropoietin (Ortho Pharmaceuticals, Raritan, N.J.) was given subcutaneously at a dose of 50 U per kilogram of body weight three times a week. A complete blood count was performed every 10 to 14 days until reticulocytosis occurred and the target hematocrit, which was 10 percent above base line, was reached (as it was in seven of the eight patients) (Table 2). The duration of treatment ranged from 6 to 10 weeks. Plasma and red-cell volumes and the hemodynamic response to orthostatic stress were measured in Patients 1, 2, 3, 7, and 8 in the hospital and in Patients 4, 5, and 6 while they were outpatients. The trial of erythropoietin was initiated as soon as possible after the orthostatic hypotension and red-cell deficit were documented. The plasma and red-cell volumes were remeasured and hemodynamic measurements were repeated at least 48 hours (but no longer than one week) after the last dose of erythropoietin was given. Patients were given a diet containing 120 to 150 mmol of sodium per day in the hospital and received instructions for maintaining sodium intake in this range at home.

Plasma glucose concentrations were measured three or four times daily in the patients with diabetes, and the dose of insulin was adjusted to provide optimal glycemic control.

Measurement of Plasma and Red-Cell Volumes

The plasma volume was determined from the iodine-125 distribution space,[12] and the red-cell volume was calculated from the plasma volume and the hematocrit according to the method of Nusynowitz and Blumhardt.[13] We measured the red-cell mass in some

Table 2. Effects of Erythropoietin on Blood Pressures in the Supine and Standing Positions in Patients with Orthostatic Hypotension.*

Patient No.	Duration of Erythropoietin Therapy	Hematocrit		Blood Pressure Supine		Blood Pressure Standing		Heart Rate Supine		Heart Rate Standing	
		before	after	before	after	before	after	before	after	before	after
	wk			mm Hg				beats/min			
1	7	0.33	0.40	115/66	134/84	71/42	86/58	64	69	88	83
2	9	0.29	0.42	146/96	133/86	82/53	92/52	92	84	130	119
3	6	0.30	0.40	118/70	116/70	76/46	81/57	88	99	104	111
4	8	0.33	0.47	144/66	193/79	80/36	116/58	68	61	68	60
5	8	0.35	0.47	111/66	100/59	86/51	95/60	65	59	73	70
6	8	0.40	0.52	133/87	155/97	105/62	148/104	78	84	85	92
7	6	0.37	0.48	105/61	115/69	71/31	74/44	64	65	137	132
8	10	0.33	0.45	138/76	165/86	78/46	110/71	77	75	85	76
Mean ±SD		0.34±0.04	0.45±0.04†	126±16/74±12	139±31/79±12	81±11/46±10	100±24‡/63±18‡	75±11	76±14	96±25	93±25

*"Before" and "after" refer to before and after treatment with erythropoietin.

†$P<0.005$ for the comparison with the pretreatment value.

‡$P<0.01$ for the comparison with the pretreatment value.

patients with an independent method — the dilution of endogenous red cells labeled with sodium chromate Cr 51.[14] The agreement between the two methods was good.

Statistical Analysis

The results are presented as means ±SD. The statistical significance of the differences was assessed with the two-tailed paired t-test.

Results

Most of the patients with orthostatic hypotension performed poorly on at least one vasomotor-reflex test or had other evidence of autonomic neuropathy, such as absent autonomic surface potentials (Table 1). The increase in plasma norepinephrine concentrations with standing (value standing minus value supine) was lower than normal in five patients (less than 140 pg per milliliter [0.83 nmol per liter]).

The mean (±SD) hematocrit before fludrocortisone therapy was 0.35±0.04, and it was 0.34±0.04 while the patients were receiving fludrocortisone just before erythropoietin treatment was initiated. The mean corpuscular volume averaged 88.9±3.1 μm^3. The serum iron level was normal (86±39 μg per deciliter [15.3±6.7 μmol per liter]). The serum ferritin level was normal in five of the six patients in whom it was measured, and serum vitamin B_{12} and folic acid concentrations were normal in all five patients tested. The red-cell volume, as measured indirectly,[12,13] was below the lower limits of normal (25 ml per kilogram for men and 20 ml per kilogram for women) in all the patients. The results were confirmed in six patients by measuring the distribution space of ^{51}Cr-labeled endogenous red cells.[14] The plasma volume, by contrast, was decreased (less than 30 ml per kilogram) in only one patient.[5] The serum erythropoietin level was within the normal range (5 to 20 mU per milliliter) in six of the seven patients in whom it was measured; one patient (Patient 1) had a markedly elevated value (128 mU per milliliter).

Erythropoietin therapy increased the mean hematocrit from 0.34±0.04 to 0.45±0.04 ($P<0.005$) and increased the red-cell volume from 16.8±3.9 to 25.3±3.1 ml per kilogram ($P<0.005$). The plasma volume, however, was virtually unchanged (Table 3). The mean weight of the patients before and after erythropoietin therapy was 63.4±12.3 and 64.1±12.2 kg, respectively.

The mean systolic blood pressure while the patients were standing increased from 81±11 to 100±24 mm Hg ($P<0.01$) and the mean diastolic blood pressure increased from 46±10 to 63±18 mm Hg ($P<0.01$) after erythropoietin therapy (Fig. 1). Before erythropoietin therapy, the mean heart rate increased from 75±11 to 96±25 beats per minute when the patients changed from the supine to the upright position; after erythropoietin therapy the heart rates were 76±14 and 93±25 beats per minute, respectively. The mean blood pressure while supine was not significantly different after erythropoietin therapy from the value before treatment (139±31/79±12 vs. 126±16/74±12 mm Hg). However, hypertension while supine developed in three of the eight patients during the administration of erythropoietin (Fig. 1). There were no other adverse drug effects. Although there was no correlation between a patient's base-line performance on most autonomic-function tests and the hemodynamic response to erythropoietin, there was a tendency for patients with a blunted response to the Valsalva maneuver at base line to have a greater increase during erythropoietin treatment in blood pressure while supine ($r = -0.72$, $P = 0.07$). There was no correlation between the effect of erythropoietin on the red-cell volume and its hemodynamic effects.

Table 3. Hematologic Effects of Erythropoietin in Patients with Orthostatic Hypotension.*

Erythropoietin	Hematocrit	Plasma Volume	Red-Cell Volume
		ml/kg	
Before treatment	0.34±0.04	39.5±8.4	16.8±3.9
After treatment	0.45±0.04	40.8±6.4	25.3±3.1†

*The results are given as means ±SD.
†$P<0.005$ for the comparison with the pretreatment value.

All patients were asked at the end of the trial to assess the efficacy of erythropoietin; six of the eight stated that their orthostatic dizziness had definitely improved. Four of the patients who described improvement had a recurrence of orthostatic dizziness two or three months after the discontinuation of erythropoietin.

Discussion

We found that the administration of erythropoietin increased blood pressure in the upright posture in patients with orthostatic hypotension. Since autonomic reflexes fail to regulate vascular tone appropriately in patients with orthostatic hypotension, their blood pressure tends to fluctuate widely according to changes in blood volume.[15] The pressor effect of erythropoietin was probably due to the increased production of red cells and the expansion of red-cell mass, although erythropoietin may have vascular effects as well.[16-18] The latter may be due to increased hemoglobin concentrations or increased blood viscosity. Hemoglobin binds nitric oxide and may therefore inhibit the action of this endogenous vasodilator.[19]

The usual approach to the treatment of patients with orthostatic hypotension is to expand the plasma volume by administering fludrocortisone. Many patients with autonomic neuropathy, however, have a normal plasma volume[15] and become hypervolemic during long-term therapy with fludrocortisone. Hypertension while supine, edema, or congestive heart failure may ensue, particularly when high doses of fludrocortisone (0.4 mg per day or more) are adminis-

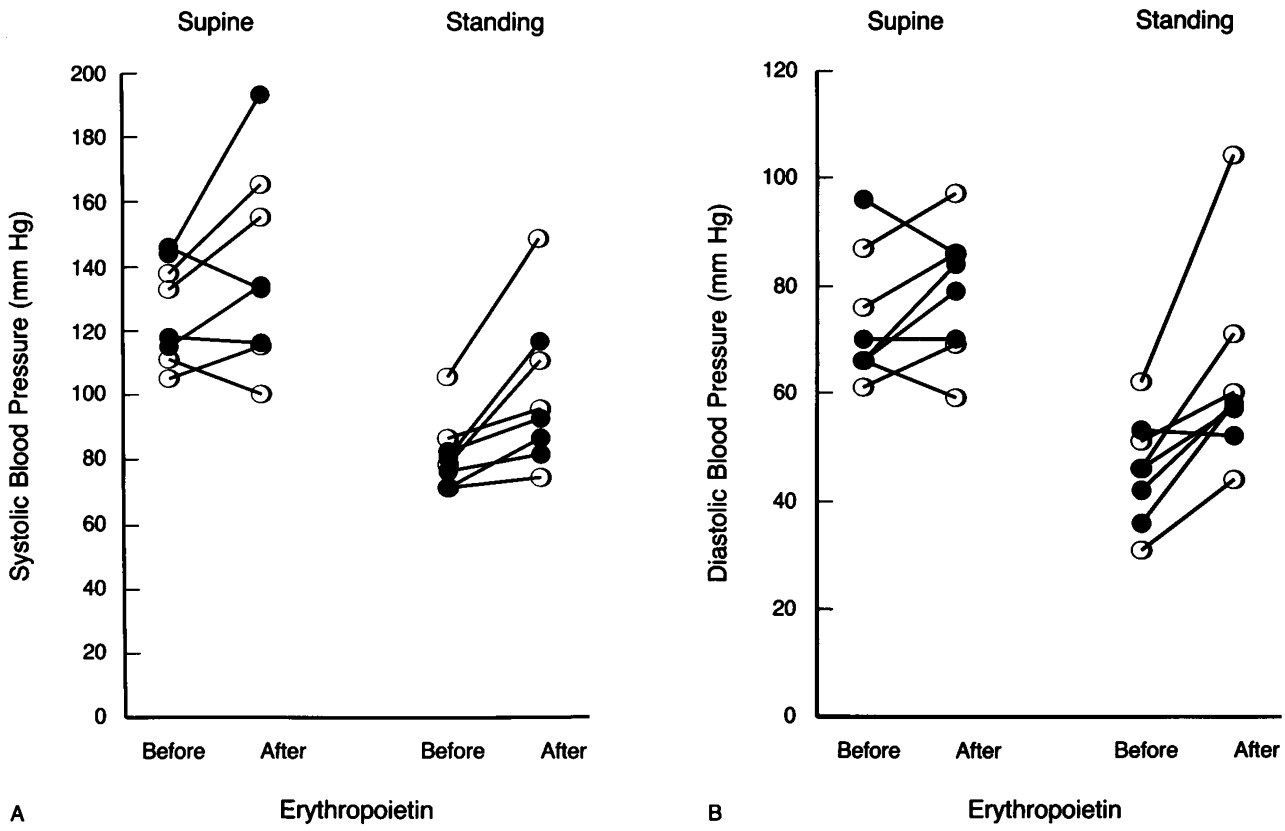

Figure 1. Effect of Erythropoietin on Blood Pressure in Patients with Orthostatic Hypotension.
Solid circles represent the patients with type I diabetes mellitus. Erythropoietin therapy increased systolic ($P<0.01$) and diastolic ($P<0.01$) blood pressure while standing, but did not significantly alter blood pressure while supine.

tered.[15,20] We postulated that erythropoietin would correct the deficit in red-cell mass without causing hypervolemia. Although our studies of plasma and red-cell volumes indicated that erythropoietin therapy did not overcorrect the red-cell deficit, hypertension while supine nevertheless developed in three patients.

The cause of the decreased red-cell volume that occurs in some patients with autonomic neuropathy is unknown. Although most of our patients had normal serum erythropoietin concentrations, the concentrations probably would have been high if the red-cell deficit had been appropriately recognized by the kidneys. A normal serum erythropoietin level may therefore be inappropriately low. Biaggioni et al. found that the serum erythropoietin level was lower in patients with anemia due to autonomic failure than in patients with iron-deficiency anemia (unpublished data). They postulated that decreased erythropoietin secretion in patients with autonomic neuropathy is a manifestation of renal denervation, perhaps linked to the decrease in renin secretion that also occurs in this disorder.[1,21]

The only adverse effect of erythropoietin was hypertension in the supine position, which developed in three patients even though we excluded patients with a propensity for such hypertension (a blood pressure greater than 150/100 mm Hg). This restriction limits the usefulness of erythropoietin therapy, since at least 50 percent of patients with autonomic neuropathy already have hypertension while supine or acquire it when given fludrocortisone. We continued to give the patients a low dose of fludrocortisone during the trial of erythropoietin, since we thought it unlikely that erythropoietin, which is expensive and must be taken parenterally, would ever replace fludrocortisone as first-line therapy for patients with orthostatic hypotension. We therefore designed this study to determine whether combined treatment with erythropoietin and fludrocortisone was better than treatment with fludrocortisone alone. Our results indicate that this is the case and suggest that erythropoietin in combination with low-dose fludrocortisone may be preferable to fludrocortisone alone in patients whose red-cell volume is decreased. Most of the patients we studied had definite improvement in their orthostatic symptoms and an improved sense of well-being after the reversal of their red-cell deficit. Similar observations have been made by another group of investigators (Biaggioni I: personal communication). Additional studies of larger numbers of patients are needed to determine whether erythropoietin plus a low dose of fludrocortisone is more beneficial than a higher dose of fludrocortisone. Until such information becomes available, we recommend that fludrocortisone remain

the primary mode of treatment and erythropoietin be reserved for patients whose hypotension fails to respond to mineralocorticoid therapy. Moreover, erythropoietin should only be used in patients with anemia or a documented deficit in red-cell volume.

In summary, erythropoietin increases blood pressure in the upright posture in patients with autonomic neuropathy and may be useful therapeutically in patients who have an inadequate response to mineralocorticoid therapy.

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