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Cardiovascular consequences of correction of the anemia of renal failure with erythropoietin

SUSAN K. FELLNER, ROBERTO M. LANG, ALEX NEUMANN, CLAUDIA KORCARZ, and KENNETH M. BOROW

Sections of Nephrology and Cardiology, Department of Medicine, University of Chicago, Chicago, Illinois, USA

Cardiovascular consequences of correction of the anemia of renal failure with erythropoietin. The purpose of this study was to define the physiologic responses of the heart and peripheral circulation to chronic anemia using noninvasive measurements while eliminating confounding biochemical, pharmacologic and physiologic variables. Stable chronic hemodialysis patients were studied at the University Hospital based chronic dialysis unit and echocardiography laboratory before and after therapy with human recombinant erythropoietin (rHuEPO). Subjects included maintenance hemodialysis patients free of left ventricular regional wall motion abnormalities discernible by echocardiography, rhythm disturbance, significant valvular or ischemic heart disease. Two-dimensional echocardiograms and simultaneous targeted M-mode echocardiograms, phonocardiograms and externally acquired subclavian artery pulse tracings were used to measure whole blood viscosity, arterial blood gases and ionized calcium, complete blood count, electrolytes, creatinine, blood urea nitrogen (BUN), and inorganic phosphate. All measurements were made immediately post-dialysis before and after therapy with rHuEPO. The interval between pre- and post-rHuEPO studies was 8.3 ± 2.3 months. We found that post-dialysis hematocrit rose from 24.7 ± 0.9 to 36.4 ± 0.9%, hemoglobin from 83 ± 3 to 121 ± 3 g/liter and whole blood viscosity from 2.87 ± 0.11 to 3.71 ± 0.18 centipoise (all, $P < 0.001$ after therapy with rHuEPO). The remaining biochemical measurements did not change. Heart rate fell from 83 ± 3 to 77 ± 3 beats/min ($P = 0.013$). Left ventricular preload and afterload were not statistically different before and after rHuEPO. Total vascular resistance rose from 1313 ± 84 to 1568 ± 129 dynes · sec · cm^{-5}, $P = 0.029$. Cardiac output and cardiac index fell by 12 and 15% ($P = 0.024$ and 0.030), respectively. Left ventricular contractility assessed using load and heart rate independent indices fell after therapy with rHuEPO ($P = 0.003$) in the nine patients in whom it was measured. In conclusion, correction of the anemia of chronic renal failure in maintenance hemodialysis patients with rHuEPO reduces measurements of global left ventricular systolic function by decreasing the heart rate and contractile state without significantly altering chamber loading conditions. The net effect is a decrease in the hyperdynamic circulatory state that typically characterizes chronic anemia.

The mechanisms by which the cardiovascular system compensate for the reduced oxygen carrying capacity of chronic anemia have been a topic of investigation and controversy for nearly half a century. Studies performed in animals made anemic by infusion of high and low molecular weight dextran [1, 2] and in humans with renal failure who received blood transfusions [3] proposed that anemia is a hyperdynamic circulatory state characterized by increased cardiac output, stroke volume, preload and contractility. Further support for this premise came from investigations of cardiovascular physiology in patients whose anemia was alleviated after kidney transplantation [4, 5]. Interpretation of the results of these studies, however, is impeded by intra- and inter-patient differences in blood pressure, biochemical milieu and drugs.

The recent introduction of human recombinant erythropoietin (rHuEPO) into clinical medical practice has provided a unique opportunity to study the hemodynamic and cardiovascular responses to the correction of the anemia of renal failure. However, contemporary studies of dialysis patients treated with rHuEPO have employed models that often make mechanistic interpretation of the cardiovascular changes associated with this therapy difficult. Specifically, changes in blood ionized calcium (Ca^{2+}), potassium or pH, use of beta adrenoreceptor or calcium entry channel blocking drugs, or alterations in heart rate and loading conditions can influence myocardial performance and consequently, when not tightly controlled, generate conflicting results. For example, Verbeelen et al [6] and Paganini et al [7] reported an improvement in cardiac output (CO) and a fall in total vascular resistance (TVR) after improvement of anemia with rHuEPO. In contrast, other investigators utilizing a variety of protocols and techniques for measuring hemodynamic variables, found a fall in cardiac index and an increase in systemic vascular resistance [8–15]. Myocardial contractility has been reported to improve [10, 13] or not change [9].

Progressive myocardial dysfunction occurs in the majority of patients undergoing long–term dialysis [16–20]. The extent to which the increased myocardial work and energetic demands associated with a hyperdynamic circulatory state contributes to this cardiomyopathy is unclear. The purpose of the current prospective study was to define the physiologic responses of the heart and peripheral circulation to chronic anemia using noninvasive measurements of left ventricular loading conditions and contractile state while eliminating confounding biochemical, pharmacologic [21] and physiologic variables; only red cell mass and whole blood viscosity changed over time. In this manner it was possible to test the hypothesis that amelioration of chronic anemia in patients with renal failure lessens a hyperdynamic circulatory state by decreasing ventricular loading conditions and contractile state. The net result of these changes would be a decrement in myocardial work.

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Methods

Patients

The current investigation consisted of 18 stable hemodialysis patients (13 female and 5 male) ranging in age from 21 to 68 (45 ± 4) years who had technically adequate ultrasound images. Causes of end-stage renal disease were nephrosclerosis (6 patients), lupus nephritis (4 patients), diabetic nephropathy (3 patients), glomerulonephritis (2 patients) chronic interstitial nephritis (1 patient) and polycystic kidney disease (1 patient). Duration of hemodialysis was 10 to 124 months (mean 40 ± 19 months). No study patient had regional wall motion abnormalities on two-dimensional echocardiographic examination, cardiac rhythm disturbances or a history of ischemic heart disease or clinically significant valvular heart disease. None had taken beta adrenoreceptor or calcium channel blocking agents or positive inotropic drugs within one week of the study day. None experienced intercurrent illness or change in biochemical control during the study period. All patients had a predialysis hematocrit of 25% or less. Thirty-one patients were originally entered into the study; thirteen failed to complete the protocol because of death (2 patients), renal transplantation (4 patients), intercurrent illness (3 patients), development of myocardial ischemia (2 patients) or refusal to participate in the second study (2 patients).

rHuEPO administration

rHuEPO (AMGEN, Thousand Oaks, California, USA), approximately 50 U/kg body wt, was administered to each patient through the dialysis venous line at the end of each dialysis until the hematocrit achieved a stable prehemodialysis level of ≥30%. Thereafter, the dose of rHuEPO was adjusted to maintain this value. Iron stores were assessed monthly and iron supplementation was provided with parenteral iron dextran (Imferon, Fissons) or oral iron in patients who had demonstrated hypersensitivity to iron dextran.

Study conditions

Immediately after a regular hemodialysis and ultrafiltration utilizing bicarbonate dialysate, blood was drawn from the arterial limb of the dialysis fistula for biochemical measurements and blood gases. Thus, all blood values reflected the immediacy of dialysis and ultrafiltration. Cardiovascular studies were always performed within two hours of dialysis in order to ensure constancy of the biochemical milieu and isovolemia. We have reported previously on the high level of hemodynamic and biochemical stability achieved during this initial post-dialysis period [22]. Blood determinations were made in the clinical chemistry and pulmonary function laboratories of the University of Chicago Medical Center. Blood viscosity was measured with a cone plate viscometer (Wells-Brookfield, model LVT-DV2, Stoughton, Massachusetts, USA). The interval between pre- and post-rHuEPO studies was 8.3 ± 2.3 months. Patients maintained a stable predialysis hematocrit of 30% or more for at least two months before the second study was performed.

In order to assess the effect of therapy with rHuEPO on blood pressure, pre- and post-dialysis weights and blood pressures measured with a sphygmomanometer were recorded for every dialysis for a period of at least two months prior to initiation of therapy with rHuEPO and for at least four months after achieving target hematocrit.

Data acquisition

Ultrasound evaluation was performed using a 2.5 MHz imaging transducer and a 1.9 MHz Pedof transducer (Hewlett-Packard, Andover, Massachusetts, USA). Two-dimensional echocardiographic images of the left ventricle were acquired during held end-expiration using (1) a parasternal short axis transducer position in which the ultrasound beam was directed at the mid equatorial plane of the ventricle (that is, just off the tip of the anterior leaflet of the mitral valve), and (2) an apical four chamber view for determination of long axis (L) dimension. Simultaneous two-dimensionally targeted M-mode echocardiograms, phonocardiograms and externally-acquired subclavian artery pulse tracings were recorded in conjunction with measurements of systemic blood pressure (Dinamap Vital Signs Monitor, model #946P, Critikon, Inc., Tampa, Florida, USA). The subclavian pulse tracings were calibrated such that peak systolic blood pressure was set to the peak of the tracing and arterial diastolic pressure to the nadir. Left ventricular pressures at end-systole (P_{es}) were determined by linear interpolation. This method of calibration been shown previously to be accurate for a wide range of ejection pressures and cardiac outputs [23].

In order to assess cardiac performance over a range of left ventricular loading conditions, recordings were obtained under control conditions as well as during infusion of either the alpha$_1$-specific adrenoreceptor agonist methoxamine or the vasodilator nitroprusside. Methoxamine (1 mg/min), which was used when baseline mean arterial pressure was 125 mm Hg or less, caused an increase in left ventricular systolic pressure secondary to peripheral vasoconstriction without effects on ventricular contractile state. Heart rate was maintained within a narrow range with atropine sulfate (0.005 to 0.010 mg/kg body wt). The ventricular response to arterial vasoconstriction was assessed with recordings obtained every one to two minutes until peak systolic pressure had increased 20 to 40 mm Hg above baseline. At that time infusion of methoxamine was discontinued. The peak pressor effect lasted two to five minutes. Nitroprusside was given if baseline mean arterial pressure was greater than 125 mm Hg. The infusion rate was titrated incrementally from 0.125 to 2.0 μg/kg/min until peak systolic pressure fell by 10 to 20 mm Hg from the baseline values or heart rate increased by 10 beats per minute. A control data point as well as two to four additional points were obtained during either the methoxamine or nitroprusside infusions.

Data analysis

Left ventricular end-systolic and end-diastolic minor and long axis dimensions (D_{es}, D_{ed}, L_{es}, L_{ed}, respectively) as well as wall thickness (h_{es}, h_{ed}) were measured from the echocardiographic recordings as described previously [22]. The left ventricular percent fractional shortening (%ΔD) was calculated as $(D_{ed} - D_{es})/D_{ed}$. The left ventricular ejection time (ET) was measured from the subclavian pulse tracing. The rate-corrected mean velocity of fiber shortening (Vcf_c) was calculated as:

$$Vcf_c = \frac{\frac{(\%\Delta D)}{ET}}{\sqrt{RR}}$$

where RR equals the interval between cardiac cycles determined from the electrocardiogram. Left ventricular circumferential end-systolic wall stress (σ_{es}) was calculated using the formula:

σ_{es} = [Pressure][Geometric factor]

$$= [P_{es}] \frac{D_{es}}{2h_{es}} \left(1 - \frac{D_{es}^3}{2L_{es}^2(D_{es} + h_{es})}\right) (1.35)$$

where σ_{es} is in g/cm; P_{es} is in mm Hg; D_{es}, L_{es} and h_{es} are in cm; and 1.35 is a conversion factor. Previous studies using this integrated noninvasive approach to data analysis have shown minimal inter- and intra-observer variability [24].

Left ventricular contractile state was assessed using the heart rate and load-independent relationship between circumferential end-systolic wall stress and rate-corrected velocity of fiber shortening (σ_{es} – Vcf_c). This relationship was determined by linear regression analysis (least squares method) using a minimum of three data points acquired over a range of left ventricular loading conditions generated by either methoxamine or nitroprusside. Comparisons of σ_{es} – Vcf_c data obtained pre- and post-rHuEPO therapy were made by the determination of Vcf_c values at a common level of end-systolic circumferential wall stress. The midpoint of the region of overlap for these two lines was selected as the point of afterload (that is, σ_{es}) commonality. The difference in Vcf_c values (ΔVcf_c) was calculated as Vcf_c (pre) minus Vcf_c (post). Patients were excluded from this analysis if: (1) the heart rate changed by more than 10 beats/min during nitroprusside or methoxamine administration, (2) the range of circumferential end-systolic wall stress was less than 15 g/cm^2 with load manipulation, or (3) the plot of the σ_{es} – Vcf_c line obtained before and after therapy with rHuEPO did not produce a region of overlapping data. This latter exclusion criterion eliminated the possibility of errors due to the use of extrapolation of data.

Left ventricular stroke volume (SV) was calculated as the product of aortic annular cross sectional area measured by two-dimensional echocardiography and flow velocity integral acquired through the aortic valve using continuous wave doppler. Cardiac output was calculated by multiplying the heart rate and stroke volume. Stroke volume index and cardiac index were calculated by dividing by body surface area. Total vascular resistance (TVR, dyne · sec · cm^{-5}) was determined as:

$$TVR = \frac{\bar{Pao}}{CO} (80)$$

where $\bar{Pao}$ is mean aortic pressure (mm Hg) and CO is cardiac output (liter/min). Left ventricular wall mass index was calculated with the formula [25]

$$0.8\,[1.04\,(D_{ed} + 2h_{ed})^3 - D_{ed}^3] + 0.6/\text{body surface area}$$

Statistics

Each patient served as his/her own control. Comparisons were done with a paired *t*-test in which $P < 0.05$ was considered statistically significant. Group data are expressed as mean values ± standard error.

Table 1. Summary of biochemical measurements

Variables	Pre-EPO	Post-EPO	*P* value
Hemoglobin *g/liter*	83 ± 3	121 ± 3	<0.001
Hematocrit %	24.7 ± 0.9	36.4 ± 0.9	<0.001
Sodium *mmol/liter*	140.4 ± 1.2	138.9 ± 0.6	0.25
Potassium *mmol/liter*	3.8 ± 0.1	3.8 ± 0.2	0.69
Blood urea nitrogen *mmol/liter urea*	11.6 ± 1.5	12.5 ± 1.0	0.56
Creatinine *μmol/liter*	688 ± 61	728 ± 50	0.46
Calcium *mmol/liter*	2.65 ± 0.03	2.65 ± 0.04	0.86
Phosphate *mmol/liter*	1.1 ± 0.07	1.2 ± 0.07	0.46
Ca^{2+} *mmol/liter*	1.21 ± 0.03	1.26 ± 0.05	0.76
pH	7.44 ± 0.01	7.44 ± 0.01	0.95
pO_2 *Torr*	93 ± 2	93 ± 2	0.58
pCO_2 *Torr*	37 ± 1	37 ± 1	0.69
Viscosity *centipoise*[a]	2.87 ± 0.11	3.71 ± 0.18	<0.001

Values are mean ± SEM.
[a] $N = 14$; all other values are for $N = 18$ patients

Results

Hematologic data

Hematocrit and hemoglobin values that defined study entry criteria and end points were measured predialysis with regular monthly laboratory work. However, because all blood measurements obtained at the time of echocardiographic imaging were made immediately after dialysis and ultrafiltration, hemoglobin and hematocrit values reflected the effect of hemoconcentration. Following treatment with rHuEPO, post-dialysis hematocrit rose from 24.7 ± 0.9 to 36.4 ± 0.9% and hemoglobin from 83 ± 3 to 121 ± 3 g/liter. Whole blood viscosity increased from 2.87 ± 0.11 to 3.71 ± 0.18 centipoise, $P < 0.001$ (Table 1) in the 14 patients in whom it was measured. Hematocrits were stable at >30% and hemoglobin >100 g/liter for at least two months prior to acquisition of post-rHuEPO hemodynamic measurements.

Biochemical data

Electrolytes, Ca^{2+}, phosphate, arterial blood gases, creatinine and blood urea nitrogen (BUN) were not different before and after therapy with rHuEPO (Table 1).

Body weights

There were no differences in post-dialysis body weights before or after therapy with rHuEPO (61.5 ± 3.6 vs. 61.0 ± 4.2 kg, $P = 0.57$) on the days of the echocardiographic studies. Furthermore, pre- and post-dialysis body weights recorded for every dialysis in the two months prior to initiation of therapy with rHuEPO until the completion of the study did not differ (Fig. 1).

Cardiovascular hemodynamics

The heart rate fell from 83 ± 3 to 77 ± 3 beats/minute, $P = 0.013$ (Table 2).

Arterial blood pressure during the two months prior to

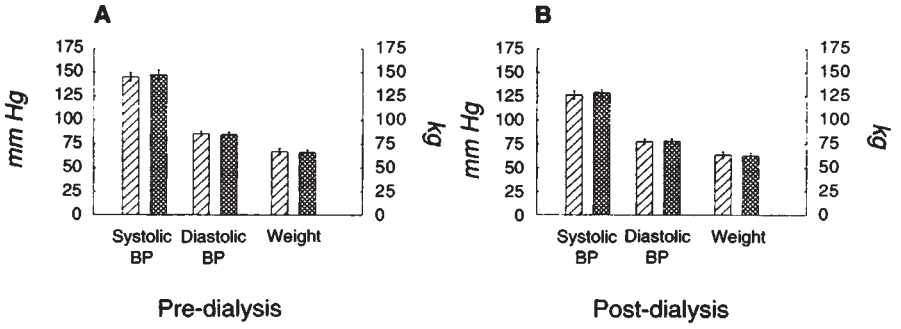

Fig. 1. *Values for arterial systolic and diastolic blood pressures (BP) as well as body weights obtained before and after hemodialysis.* Diagonal lines represent pre-erythropoietin (rHuEPO) measurements; hatched lines are post-rHuEPO.

Table 2. Cardiovascular hemodynamics

Variables	Pre-EPO	Post-EPO	*P* value
Heart rate *beats/min*	83 ± 3	77 ± 3	0.013
Arterial blood pressure			
Peak systolic *mm Hg*	141 ± 6	146 ± 7	0.42
Diastolic *mm Hg*	82 ± 5	84 ± 5	0.61
Mean *mm Hg*	97 ± 3	106 ± 5	0.22
End systolic *mm Hg*	120 ± 4	127 ± 7	0.25
Left ventricular preload			
Ded *cm*	4.4 ± 0.1	4.3 ± 0.2	0.13
Left ventricular afterload			
End-systolic wall stress *g/cm²*	136 ± 16	144 ± 21	0.42
Total vascular resistance *dynes · sec · cm⁻⁵*	1313 ± 84	1568 ± 129	0.029
Overall LV systolic performance			
Percent fractional shortening	0.30 ± 0.03	0.29 ± .03	0.42
Cardiac output *liter/min*	6.6 ± 0.4	5.8 ± 0.3	0.024
Cardiac index *l/min/M²*	4.0 ± 0.3	3.4 ± 0.2	0.030
Stroke volume *cm³/beat*	80 ± 4	77 ± 4	0.51
Stroke volume index *cm²/beat/M² BSA*	48 ± 3	46 ± 2	0.45
Left ventricular contractility			
Vcf_c *(circ/sec)*[a]	0.96 ± 0.07	0.85 ± 0.07	0.003

Values are mean ± SEM. Abbreviations are: EPO, erythropoietin; Ded, left ventricular end-diastolic minor axis dimension.

[a] Vcf_c, rate corrected velocity of fiber shortening at a common left ventricular afterload for 9 patients

achieving a target hematocrit of 30% was not different from that recorded for three months thereafter. This was true for comparisons performed using both pre and post-dialysis values (Fig. 1). However, six of 18 patients (33%) developed interdialytic hypertension that required a modest increase in the dose of angiotensin converting enzyme inhibitor drugs (enalapril, lisinopril) or the addition of a calcium channel blocking agent (nifedipine) to maintain normotension. The latter drug was discontinued at least one week before echocardiographic studies. Of those who became hypertensive, four of six had renal failure from nephrosclerosis.

Left ventricular preload, as assessed by end diastolic minor dimensions, did not change significantly (4.4 ± 0.1 cm to 4.3 ± 0.2 cm, $P = 0.13$).

Left ventricular afterload, measured as circumferential end-systolic wall stress (σ_{es}), was unchanged (136 ± 16 vs. 144 ± 21 g/cm², $P = 0.42$).

Total vascular resistance rose from 1313 ± 84 dynes · sec · cm^{-5} to 1568 ± 129 dynes · sec · cm^{-5}, $P = 0.029$.

Left ventricular wall mass index was unchanged after therapy with rHuEPO (143 ± 12 g/m² vs 141 ± 10 g/m², $P = 0.52$).

Overall left ventricular systolic performance changed variably depending upon the parameter measured. Percent fractional shortening, stroke volume and stroke volume index were unchanged. However, cardiac output and cardiac index fell by approximately 14% ($P = 0.024$ and 0.030, respectively) reflecting, at least in part, the 7% decline in heart rate that occurred following correction of anemia.

Left ventricular contractility was assessed in the nine patients who fulfilled the stringent criteria for determination of Vcf_c at a common level of afterload. These nine patients did not differ from the remaining nine study patients in age, etiology of renal failure, duration of hemodialysis or medications. Three of these nine patients and four of the remaining nine patients took an angiotensin converting enzyme inhibitor for blood pressure control both before and after therapy with rHuEPO. Data obtained from one of our study patients illustrate the method by which this relationship is used as a measurement of left ventricular contractility (Fig. 2). Contractile state diminished ($P = 0.003$) following correction of anemia (Table 3). Figure 3 demonstrates the relationship between change in hematocrit and change in Vcf_c in these nine patients.

Discussion

Our data demonstrate that correction of the anemia of chronic renal failure with the administration of rHuEPO reduces measurements of global left ventricular systolic function (such as, cardiac output) as well as contractile state. End diastolic dimension, an index of preload, did not change significantly. This was an expected finding since these measurements were made immediately after ultrafiltration, a maneuver that would tend to obliterate predialysis alterations in preload. Our study design avoided the pitfalls that have clouded interpretation of previous efforts at examining the hemodynamic consequences of improvement of anemia in dialysis patients. Specifically, we tightly controlled post-dialysis volume, biochemical milieu and drugs that might have cardiovascular effects. The current study is the first to use a load and heart rate independent measurement of left ventricular contractility.

At any moment in time, overall left ventricular systolic performance reflects the net effects of preload, afterload, heart rate and contractility. Isolated increases in heart rate, preload and contractility and a fall in afterload improve cardiac output whereas changes of these variables in the opposite direction diminish cardiac output. Thus, unless these hemodynamic

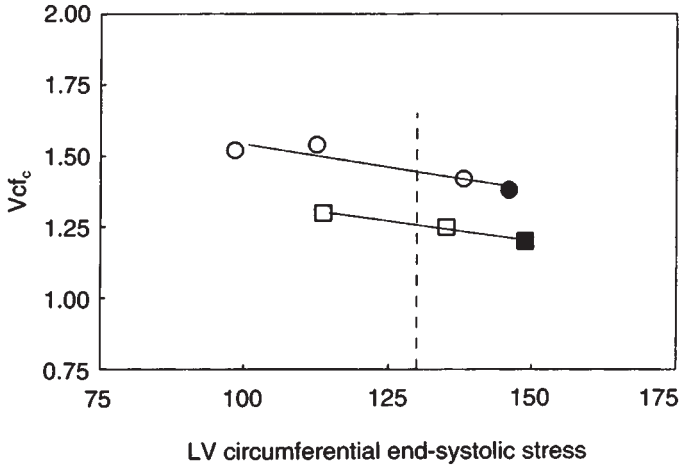

Fig. 2. *Data for the left ventricular (LV) circumferential end-systolic wall stress (g/cm²) versus the rate corrected velocity of fiber shortening (Vcf_c, circumferences/s) relation obtained from one of our study patients.* The pre-erythropoietin (rHuEPO) points are shown as circles, the post-rHuEPO points by squares. Shaded points were acquired under control conditions while open points were obtained during afterload alteration with nitroprusside or methoxamine. The vertical dashed line demonstrates the level of end-systolic wall stress that was used for comparison of pre and post-rHuEPO data.

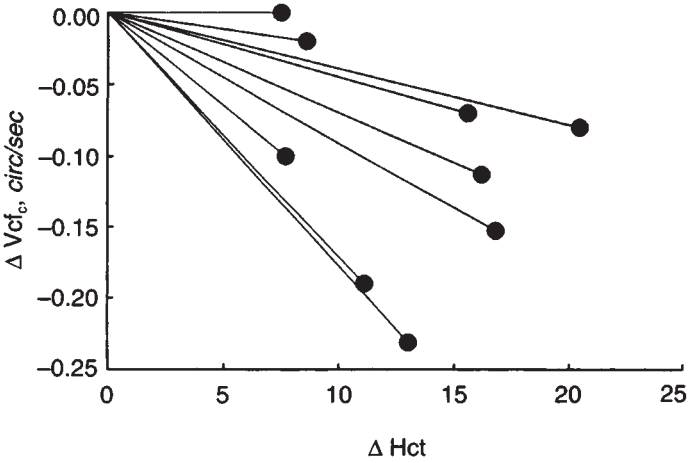

Fig. 3. *Plot of the relationship between the change in hematocrit (ΔHct) and change in left ventricular contractility (ΔVcf_c) in the nine patients who underwent afterload manipulation with methoxamine or nitroprusside.* Correction of anemia was associated with a decrease in LV contractile state.

Table 3. Rate corrected velocity of circumferential fiber shortening (Vcf_c) (circ/sec) at a common level of afterload

Patient	Pre-EPO	Post-EPO	Delta
1	1.11	1.01	−0.100
2	0.87	0.79	−0.080
3	0.80	0.80	0.000
4	0.59	0.48	−0.113
5	0.81	0.74	−0.070
6	1.07	0.92	−0.153
7	0.91	0.71	−0.195
8	1.30	1.07	−0.231
9	1.16	1.14	−0.020
Mean	0.96 ± 0.07	0.85 ± 0.07[a]	−0.11 ± 0.03[a]

[a] $P = 0.003$, post-EPO vs. pre-EPO

parameters are carefully measured, statements about the specific cardiovascular mechanisms affecting global left ventricular performance after correction of anemia may be inaccurate.

We have previously shown that myocardial contractility varies directly with blood ionized calcium (Ca^{2+}) [22]. Predialysis Ca^{2+} has been shown to be 0.96 ± 0.03 versus 1.19 ± 0.03 mmol/liter in hemodialysis patients utilizing a 1.50 mmol/liter calcium dialysate [26]. This value compares to 1.34 mmol/liter immediately after dialysis with a 1.75 mmol/liter calcium dialysis bath [22]. If hemodynamic measurements are not made in exactly the same phase of the interdialytic cycle, inter-study differences in Ca^{2+} can modify myocardial performance.

Drugs that alter heart rate, contractile state or sympathetic tone can obscure or abolish hemodynamic changes that result from correction of anemia with rHuEPO [21]. Even if there is no change in drug regimen between pre- and post-rHuEPO studies, the presence of such pharmacologic agents may prevent the expression of responses that are mediated by the sympathetic nervous system or by intrinsic changes in contractility. Many of the previous studies of the effect of rHuEPO on the heart did not control for these drugs [6, 8–11, 13]. We specifically prohibited the use of inotropic agents as well as beta adrenoreceptor and calcium channel blocking drugs for at least one week prior to each study.

A criticism of all studies that examine myocardial performance in a time dependent fashion following therapy with rHuEPO is that progression of myocardial disease from hypertension or ischemia can confound changes that result from correction of anemia. The relatively short study period (8 ± 2 months) would not be expected to be associated with clinically significant changes in cardiac performance in stable patients with well controlled blood pressure. Furthermore, we excluded from analysis patients who had developed symptomatic or objective evidence of ischemic heart disease during the treatment period. This allowed the study to remain focused on the physiologic issues related to the correction of anemia. A criticism of the current study is that only nine of the eighteen patients met the stringent technical criteria for inclusion in the analysis of Vcf_c and logically raises the question of bias. That these nine patients did not differ from the group as a whole in gender, race, age, etiology of renal disease, duration of hemodialysis or use of antihypertensive drugs confirms lack of segregation of a subpopulation of patients.

We, like others, have noted an increase in blood pressure in about one third of dialysis patients after therapy with rHuEPO [27]. Increases in whole blood viscosity and reversal of hypoxia induced vasodilatation have been suggested as possible causes of increases in blood pressure [27]. However, while a rise in viscosity and systemic vascular resistance is a nearly universal finding in patients whose anemia is corrected with rHuEPO, the development of hypertension is not. It has been suggested that the presence of a mismatch between increased TVR and reduced cardiac output identifies those who become hypertensive [27]. In our study, there was no correlation between changes in cardiac output after rHuEPO and the development of hypertension.

What is the physiologic basis for the hemodynamic responses

to anemia? The hyperdynamic circulatory changes of anemia are characterized by increased heart rate and cardiac output, augmented myocardial contractility and a fall in systemic vascular resistance. It is possible that anemia stimulates humerally-mediated positive chronotropic and inotropic responses leading to primary increases in left ventricular contractility, heart rate and cardiac output. Alternatively, a reduction in systemic vascular resistance from hypoxic vasodilatation and reduced viscosity may cause a secondary enhancement of overall myocardial performance. It is unlikely that this latter explanation alone delineates the compensatory cardiovascular responses to anemia since it would not explain the enhanced contractile state present prior to amelioration of anemia with rHuEPO.

Cardiovascular disease is the leading cause of death in patients undergoing maintenance dialysis [28]. Pre-existing hypertension and coronary atherosclerotic heart disease constitute a major proportion of the cardiomyopathies of the renal failure population [19, 20, 29]. The contribution of arteriovenous fistulas, intermittent volume overload and anemia to progressive myocardial disease is not known with certainty. However, our study shows that correction of anemia in patients undergoing chronic dialysis results in a significant reduction in two of the three major determinants of myocardial energy demand (that is, heart rate and contractility) without altering the third (that is, LV systolic load). This may favorably influence the progression of heart disease in these patients. Reversal of left ventricular hypertrophy after therapy with rHuEPO has been demonstrated in several studies [10, 30]. In the current investigation, there was no change in left ventricular wall mass index. This may reflect the relatively short duration of follow-up in our study patients. The potential benefits of correction of the hyperdynamic circulatory state of anemia must be balanced against the theoretical deleterious effects of worsening of blood pressure control in some patients, higher whole blood viscosity and increased systemic vascular resistance. Whether rHuEPO ultimately will improve long-term prognosis regarding cardiovascular disease in patients undergoing long-term dialysis is not yet known.

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Reprint requests to Susan K. Fellner, M.D., Section of Nephrology, MC5100, University of Chicago, 5841 South Maryland Avenue, Chicago, Illinois 60637, USA.

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