Hemoglobin cycling in hemodialysis patients treated with recombinant human erythropoietin

STEVEN FISHBANE and JEFFREY S. BERNS

Winthrop-University Hospital, Mineola, New York; and Renal, Electrolyte, and Hypertension Division, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

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Background. Treatment with recombinant human erythropoietin (rHuEPO) has been a major advance for the management of anemia in patients on hemodialysis. Therapy, however, is often observed to be associated with recurrent cyclic fluctuations in hemoglobin levels. The purpose of this analysis was to describe the phenomenology of hemoglobin cycling during rHuEPO treatment.

Methods. Data were analyzed for 281 hemodialysis patients treated at Winthrop-University Hospital Dialysis Centers between 1998 and 2003. Eligible patients' first full 1-year period with less than 10 hospital days was studied. Hemoglobin cycling (cycles with amplitude >1.5 g/dL and duration >8 weeks) and excursions (half of one full cycle) were analyzed.

Results. Greater than 90% of patients experienced hemoglobin cycling. The mean number of hemoglobin excursions was 3.1 ± 1.1 per patient/year. The mean amplitude per hemoglobin excursion was 2.51 ± 0.89 g/dL. The mean duration of hemoglobin excursions was 10.3 ± 5.1 weeks. Factors associated with initiation of up excursions included increases in rHuEPO dose (84%), intravenous iron treatment initiation or increase in dose (27%), posthospital discharge (36%), factors associated with down excursions included rHuEPO dose hold (15%) or dose reduction (62%), infection (6%), discontinuation of intravenous iron therapy (5%), and hospitalization (14%). Patients with frequent hemoglobin cycling (>two full cycles per year) were characterized as being more responsive to rHuEPO [index of EPO responsiveness (ERI) 1036 ± 659 compared to 1992 ± 701 for other patients] ($P = 0.02$).

Conclusion. Hemoglobin cycling is a common occurrence in rHuEPO-treated hemodialysis patients. It is most closely associated with frequent rHuEPO dose changes, hospitalization, and iron treatment practices.

Anemia is one of the important complications of endstage renal disease (ESRD) [1], and treatment with recombinant human erythropoietin (rHuEPO) has been

a great advance in the management of this problem [2, 3]. Treatment to achieve partial correction of patients' hemoglobin level results in improved quality of life [4] and is associated with reduced risk for mortality [5] and hospitalization [6]. However, therapy with rHuEPO is quite different than biologic erythropoietic processes; treatment involves short, intermittent, nonphysiologic bursts of plasma EPO availability which do not directly coincide either temporally or in magnitude with physiologic perturbations. It may not be surprising, therefore, that it is routinely observed that during treatment with rHuEPO in hemodialysis patients that the level of hemoglobin fluctuates greatly. More specifically, hemoglobin levels tend to rise and fall in a cyclic pattern, one that varies from patient to patient.

The phenomenon of hemoglobin cycling has not been widely studied, but may have an adverse impact on patient outcomes since wide movement of hemoglobin values is not a part of normal homeostasis. Indeed, under normal conditions, the body's oxygen sensing, EPO-producing, and erythropoietic systems are closely regulated and coordinated [7] to maintain hemoglobin levels and oxygen delivery within a narrow range. In contrast, with hemoglobin cycling, fluctuation in oxygen delivery to vital organs occurs. Repeated episodes of relative ischemia and the resultant tissue compensation in organs such as the heart may result in disordered growth signals, pathologic organ function, and suboptimal patient outcomes. Hemoglobin cycling may also complicate clinical management of hemodialysis patients as nephrologists and anemia nurse managers respond to changes in hemoglobin levels with changes in rHuEPO dosing, which may lead to more dramatic or frequent hemoglobin cycling. The purpose of this study was to describe the phenomenology of hemoglobin cycling in rHuEPO-treated hemodialysis patients, to analyze etiologic factors, to assess the impact of hemoglobin fluctuations on iron storage, and to study factors associated with a subpopulation of patients that demonstrated a greater degree of cycling.

METHODS

Subjects

All patients on chronic maintenance outpatient hemodialysis at Winthrop-University Hospital's Mineola Center between 1998 and 2003 were screened for eligibility. This time period was selected because there were no significant changes during this time in either the unit's anemia or iron treatment protocols. In addition, there were no significant changes to Medicare reimbursement policy for rHuEPO after amendment of the prior Program Memoranda AB-98-10 (published March 1998), changing aspects of the Hematocrit Measurement Audit policy.

A dataset of patients was created to allow analysis of the phenomenon of hemoglobin cycling. Patients were excluded from analysis if they survived on dialysis for less than 1 year. The first 1 year period after January 1, 1998 in which the patient had less than 10 hospital days was chosen as that patient's analysis year. Only 1 year was analyzed per patient. Subjects with no years with less than 10 hospital days were excluded from analysis because of the powerful effect of intercurrent illness on hemoglobin stability. Other reasons for exclusion included any of the following factors being present during the analysis year: no treatment with rHuEPO, transfusion of red blood cells, medication treatment as part of participation in a clinical research study, or history of gastrointestinal or other major bleeding within 6 months.

During the period of study, a protocol for rHuEPO dose adjustment was used by the hemodialysis center. Hemoglobin levels were measured every 2 weeks for all patients, including study patients. Based on the results, the protocol directed rHuEPO dose adjustments. When the hemoglobin rose above 13.5 g/dL, the dose of rHuEPO was held for 2 weeks. The dose would be resumed, reduced by 25% to 50% when hemoglobin decreased <13.0 g/dL. For hemoglobin values >12.5 g/dL, the rHuEPO dose would be reduced by 25%. No change in dose was directed for hemoglobin between 11.0 and 12.5 g/dL. When hemoglobin was <11.0 g/dL, the rHuEPO dose would be increased 25% to 50%. The protocol dose adjustments were made by an anemia nurse manager. For any decrease in hemoglobin of more than 1 g/dL in a 2-week period, the physician was contacted to evaluate for possible bleeding or hemolysis. All rHuEPO treatment was by intravenous administration at each hemodialysis treatment. Iron management was guided by individual physician judgment. Approximately 65% of patients were treated with intravenous iron, as short-term repletive courses (52% of patients) and/or as maintenance therapy (28% of patients), noting that these numbers are >100% since some patients received both repletive courses and maintenance therapy at different times during the study year.

Definitions

A hemoglobin cycle was defined as a series of measured hemoglobin levels in an individual patient that oscillated over time, in which the levels decreased or increased over time, and then reversed direction and approximately retraced the initial trajectory. The precise starting and ending hemoglobin levels might differ, the rate of change in the up and down swing might differ, but an approximate cycle would be completed. The hemoglobin cycle midpoint was defined as the hemoglobin level halfway between the high and low end of a complete cycle. Half of one hemoglobin cycle defined a hemoglobin excursion. The duration of a hemoglobin excursion was defined as the number of weeks from the high and low hemoglobin measures in the excursion. Only excursions of 4 or more weeks' duration were analyzed. The amplitude of a hemoglobin excursion was the absolute difference between hemoglobin level at the start and end of the excursion. Hemoglobin excursions with amplitude less than 1.5 g/dL were not considered to be clinically significant. Therefore, only hemoglobin excursions with amplitude greater than 1.5 g/dL were included in the analysis. The velocity of a hemoglobin excursion is the amplitude divided by the duration and expressed in g/dL/week). For a patient with hemoglobin of 13.2 g/dL, whose level decreases over 10 weeks to 10.7 g/dL, the hemoglobin excursion amplitude is 2.5 g/dL and the velocity is 0.25 g/dL/week.

Statistical analysis

Data were collected using electronic forms created in a database software program (Microsoft Access 2003) and transferred to a spreadsheet program (Microsoft Excel 2003). Statistical analyses were performed using Graphpad statistical software (San Diego, CA, USA) and SPSS package release version 10.1.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics are presented as mean with standard deviations or with 95% confidence intervals. Differences between continuous variables were compared using Student unpaired t test. A P value of less than 0.05 was considered to represent statistical significance. Responsiveness to rHuEPO treatment was assessed by creation of an index of EPO responsiveness (ERI), calculated as the weekly rHuEPO dose (units/week) divided by the hemoglobin concentration. The lower the result, the more sensitive is the response to rHuEPO, conversely a high ERI indicates relative resistance to rHuEPO erythropoietic effects. We used logistic regression to identify factors significantly associated with hemoglobin cycling. Nonsignificant covariates were removed by backward selection. A panel of demographic (age, gender, diabetes, dialysis vintage, cause of ESRD, and ethnicity/race) and clinical factors (comorbidity, hospitalizations, medications, Kt/V, urea reduction ratio, laboratory results, and

Table 1. Patient characteristics

Total study population *number*	281
Mean age *years*	61.4 ± 13.5
Gender (male:female)%	53:47
Diabetes mellitus%	39.5
Dialysis vintage *m*	29.3 ± 28.4
Ethnicity and race%	
Caucasian	63.1
African American	19.5
Hispanic	10.5
Asian	4.4
Other	2.5
Cause of end-stage renal disease %	
Diabetes mellitus	35.4
Hypertension	30.3
Chronic glomerulonephritis	14.2
Polycystic kidney disease	6.3
Other	13.8

Fig. 1. Distribution of the number of recombinant human erythropoietin (rHuEPO) dose changes per patient in 1 year.

interdialytic weight gain) were analyzed as possible univariate predictors of hemoglobin cycling.

Because of the profound effect of intercurrent illness on hemoglobin levels, a secondary analysis was conducted in which all perihospitalization periods were excluded. Specifically, hemoglobin levels during the 4 weeks before and 4 weeks after a hospitalization were removed from this secondary analysis.

RESULTS

The characteristics of the study population of 281 patients are displayed in Table 1. During the period reviewed, the mean hemoglobin level was 11.8 g/dL (95% CI 11.2-12.1 g/dL). The mean number of rHuEPO dose changes per year per patient was 6.3 ± 3.3, and the distribution of dose changes per patient is displayed in Figure 1.

Greater than 90% of patients experienced hemoglobin cycling as defined as one or more annual, full, extended cycle of amplitude >1.5 hemoglobin g/dL of a duration greater than 8 weeks. A graphic example of hemoglobin cycling in an individual patient is displayed in Figure 2. The mean number of hemoglobin excursions (half of one cycle) per patient per year was 3.1 ± 1.1 (distribution displayed in Fig. 3). The mean amplitude per hemoglobin excursion was 2.51 ± 0.89 g/dL. The distribution of hemoglobin excursion amplitudes is displayed in Figure 4. At the peak of excursions, the mean hemoglobin was 12.8 ± 1.8 g/dL, at the nadir the mean hemoglobin was 10.3 g/dL. The mean duration of a hemoglobin excursion was 10.3 ± 5.1 weeks. For up excursions (rising hemoglobin) the mean amplitude was significantly greater, 2.7 ± 0.9 g/dL, than for down excursions, 2.4 ± 0.8 g/dL ($P = 0.04$). The mean duration of up excursions was not significantly different from the duration of down excursions (10.2 ± 5.8 weeks compared to 10.5 ± 4.0 weeks
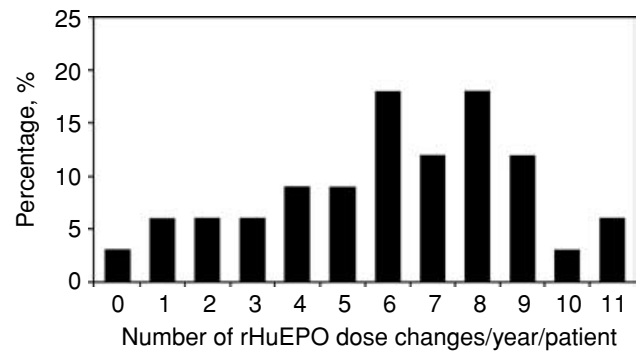
respectively) ($P = $ NS). The mean velocity of hemoglobin excursions was 0.24 g/dL/week hemoglobin change.

The relationship between a variety of demographic and clinical factors and hemoglobin cycling was studied. Clinical factors associated with initiation of up excursions included increases in rHuEPO dose (84% of cases), intravenous iron treatment initiation or increase in dose (27%), and hospital discharge within the prior 30 days (36%). Factors associated with down excursions included rHuEPO dose hold (15%), rHuEPO dose reduction (62%), infection (6%), discontinuation of intravenous iron therapy (5%), and hospitalization (14%). By multivariate analysis, changes in rHuEPO dose, changes or initiation of intravenous iron and recent hospitalization were all independent predictors of hemoglobin cycling ($P < 0.05$). Changes in rHuEPO dose leading to a hemoglobin cycle occurred with hemoglobin outside the target 11 to 12 g/dL range in 80.1% of cases. Hemoglobin cycling was not significantly affected by stable weekly maintenance intravenous iron dosing. Clinical factors not associated with cycling included other laboratory results, Kt/V or urea reduction ratio, mean intradialytic weight gain, other medications, comorbidity, or demographic factors. The effect of hospitalizations on hemoglobin trajectory was often to reset or initiate a hemoglobin cycle. Patients had a mean of 1.1 ± 1.2 hospital admissions in the year of study. With 40.4% of admissions, there was a shift in hemoglobin trajectory in the 4 weeks prior to admission, with a mean decrease of 2.8 ± 2.2 g/dL. Within 4 weeks after hospital discharge, 35% of patients entered upwards hemoglobin excursions with mean amplitude of 3.5 ± 2.4 g/dL. After discharge, the mean weekly rHuEPO dose in the 4 weeks after hospitalization was 75.5 ± 52.2% higher than in the 4 weeks prior to admission. When the perihospitalization period was excluded from analysis, the impact of rHuEPO dose changes and iron treatment as primary causes of hemoglobin cycles was amplified. Either rHuEPO dose changes or iron treatment initiation or dose increases were associated with nearly 100% of these hemoglobin excursions.
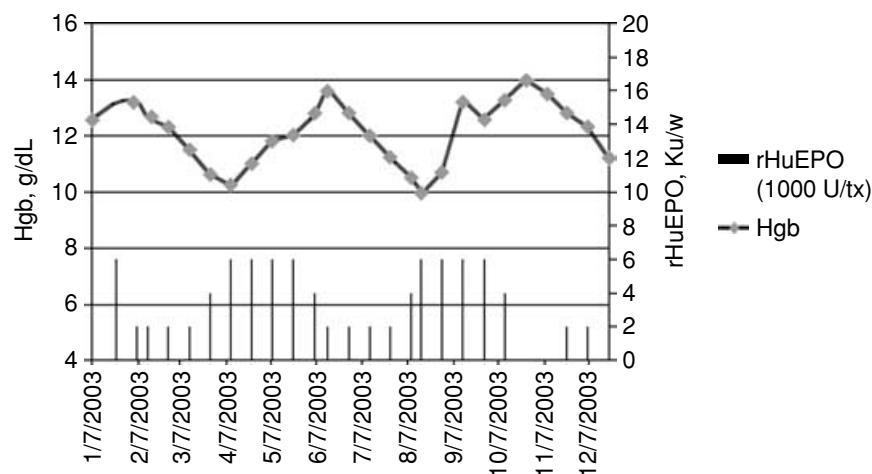
Fig. 2. A graphic example of hemoglobin (Hgb) cycling in a 59-year-old diabetic man, showing both hemoglobin and recombinant human erythropoietin (rHuEPO) dose.
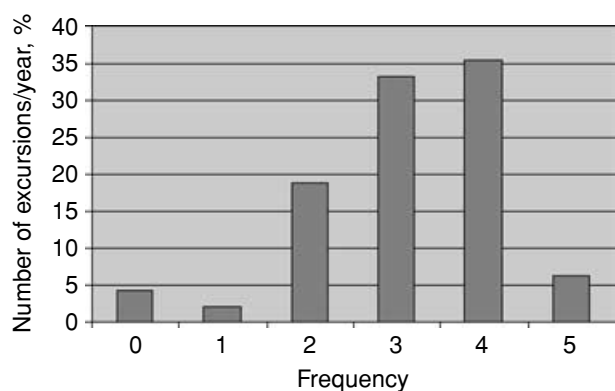

Fig. 3. Distribution of the number of hemoglobin excursions per patient in 1 year.

The impact of hemoglobin cycling on iron indices was analyzed. From the study population, 62 patients who were not on intravenous iron and who had iron indices measured in temporal association with peak and nadir hemoglobin levels during a hemoglobin excursion were studied. During up hemoglobin excursions, serum ferritin decreased by a mean of 82.2 ± 56.1 ng/mL per gram increase in hemoglobin (comparing initial and final serum ferritin) ($P < 0.0001$). During down hemoglobin excursions, serum ferritin increased by a mean of 51.7 ± 53.9 ng/mL per gram decrease in hemoglobin ($P = 0.001$). Transferrin saturation values had great variation in measured results unrelated to hemoglobin excursions; there were no statistically significant changes from beginning to end of hemoglobin excursions.

A subpopulation of patients was identified, characterized by more frequent hemoglobin cycling (>two full cycles per year). These frequent cyclers accounted for 30.1% of the entire population studied. We explored clinical factors that would explain a propensity for more frequent cycling. The mean amplitude of hemoglobin excursions was not significantly different between frequent

cyclers and others (2.6 ± 0.9 g/dL compared to 2.6 ± 1.0 g/dL, respectively) ($P =$ NS). The mean duration of a hemoglobin excursion was significantly shorter for frequent cyclers than others (9.3 ± 4.0 weeks compared to 11.1 ± 5.5 weeks, respectively) ($P = 0.007$). To evaluate rHuEPO responsiveness between the two groups, we calculated the ERI: weekly rHuEPO dose (U/week) divided by hemoglobin. Held rHuEPO doses were not included in the calculation. Patients who were frequent cyclers were significantly more responsive to rHuEPO than others, ERI 1036 ± 659 U/week/g hemoglobin compared to 1992 ± 701 U/week/g hemoglobin, respectively) ($P = 0.02$). No other clinical factors were predictive of frequent cycling behavior.

DISCUSSION

Nephrologists have often observed during rHuEPO treatment in hemodialysis patients that hemoglobin levels continually rise and fall in undulations or cycles. Despite this observation, there has been little systematic study of the phenomenon. The scientific literature contains reports of a similar and related phenomenon, population-based variability of hemoglobin results in rHuEPO-treated patients. Recently, we reported on an analysis of 987 hemodialysis patients treated at 11 American hemodialysis units. We found that hemoglobin variability was widespread, and is a clear characteristic of rHuEPO-treated hemodialysis patients [7]. In a similar study, Lacson, Ofsthun, and Lazarus [8] found that 29% of hemodialysis patients had hemoglobin levels that moved at least once to above or below a hemoglobin target range of 11 to 12 g/dL in 1 year of observation. The purpose of our current study was to analyze more precisely at the individual patient level, the movement of hemoglobin levels over time. We sought to describe hemoglobin cycling quantitatively, and to examine factors that explain the phenomenon. We have found
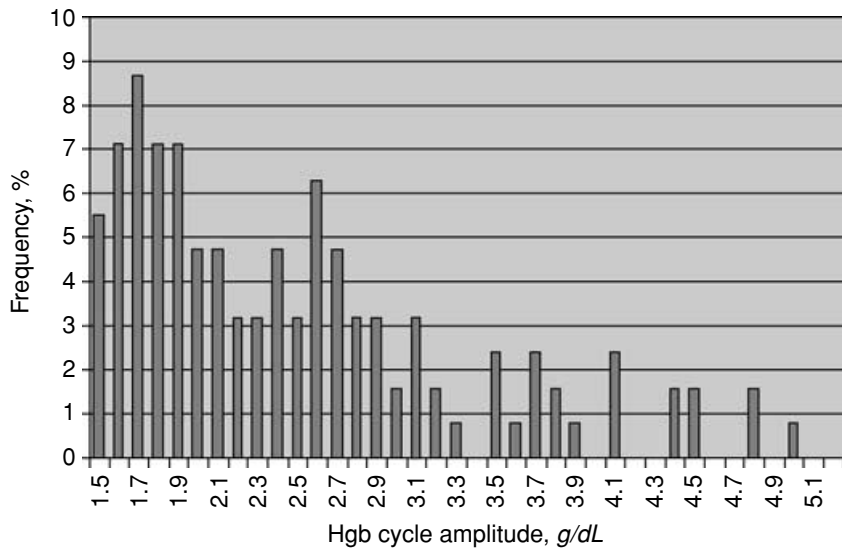
Fig. 4. Distribution of hemoglobin (Hgb) amplitude for all hemoglobin excursions. The amplitude is the difference between hemoglobin level at the beginning and end of an excursion.

that hemoglobin cycling, repeated up and down undulations of hemoglobin levels, is a common phenomenon in hemodialysis patients treated with rHuEPO. Patients' hemoglobin levels follow somewhat predictable, repeated up and down cycles, interrupted at times by intercurrent illnesses and hospitalizations.

The cause of hemoglobin cycling appears to be multifactorial. We found changes in rHuEPO dose to be the most important driver, associated with hemoglobin excursions in approximately 80% of cases. The dose of rHuEPO was changed an average of 6.1 times per patient per year in this study. Our rHuEPO dose adjustment protocol, like that used in most dialysis centers, drives dose changes when the hemoglobin level is outside of the target range [9]. The National Kidney Foundation Anemia Treatment Guidelines recommend a narrow target hemoglobin range of 11 to 12 g/dL [10]. As a result, rHuEPO dose changes, including holding of doses, are frequently required. The impact of these dose changes would ideally be a "soft landing" with the resulting hemoglobin remaining in the target range, but probably much more frequently a new trajectory of hemoglobin movement is initiated, and not infrequently hemoglobin levels outside the desired range result. As the hemoglobin level begins to move and traverses across the target range, most protocols would not require another dose change. Instead, the next dose adjustment would generally be made when the hemoglobin is out of range again, now on the opposite side of the target range. Then the entire process is repeated, in the reverse direction. In many patients the result is repeated back and forth cycling of hemoglobin levels. Furthermore, our dialysis unit, like most, has a rHuEPO dose protocol that is essentially "one size fits all." It is well known, however, that patient responsiveness to rHuEPO is highly variable; some patients respond with great sensitivity,

others may be highly resistant [11]. We found that patients who are more responsive to rHuEPO tend to have a greater degree of hemoglobin cycling. This finding may resonate with clinicians who have observed that some patients respond to rHuEPO dose increases with rapid rises in hemoglobin resulting in a need to temporarily hold doses. By the time hemoglobin result is checked again, the level may have decreased precipitously. Because of the high degree of variability in rHuEPO response, it may be unreasonable to expect the "one size fits all" dose adjustment protocol to maintain hemoglobin levels with the degree of stability attained in normal homeostasis. This may be particularly true with the use of pharmacologic rHuEPO treatment; short-acting drugs, intermittent dosing with brief "bursts" of EPO in plasma [12]. Taken together, we propose that hemoglobin cycling is primarily a result of several anemia treatment practices, including (1) a narrow target hemoglobin range; (2) rHuEPO dose adjustments; (3) patient variability in rHuEPO response, with inflexible dose adjustment protocols that do not account for patient-specific responsiveness; (4) use of pharmacologic, intermittent, intravenously administered EPO replacement using a preparation with a short half-life; and perhaps (5) the use of single hemoglobin levels obtained on a relatively frequent basis (i.e., every 2 weeks) to prompt rHuEPO dose adjustments.

Hospitalizations have a major impact on anemia management [13]. Indeed, we found that hospital admissions often initiated a hemoglobin cycle or reset an existing cycle. The effect of intercurrent illness such as vascular access infection on erythropoiesis is often a temporary relative resistance to rHuEPO treatment [14]. As a result, the hemoglobin level may decrease and the rHuEPO dose is increased in response. The blunted erythropoietic response is probably a result of cytokine induction [15]. Other factors related to hospitalization-associated

hemoglobin cycling might include missed rHuEPO doses, changes in rHuEPO dose, surgical or other invasive procedures with blood loss, and phlebotomy for laboratory tests. We found that after hospitalization that many patients had a substantial upward trajectory of hemoglobin. As patients recover from the intercurrent illness, EPO responsiveness improves and does so while patients are often on much higher doses of rHuEPO [13].

Iron status was also found to affect hemoglobin cycling. Intravenous iron therapy was associated with 27% of rising hemoglobin excursions. This was an expected finding, very consistent with literature indicating the robust efficacy of iron therapy in hemodialysis patients [16]. After a course of intravenous iron is completed, there continues to be fluxes in iron status that may last several months. The immediate impact of treatment is a repletion of iron stores, reflected best by an increase in serum ferritin [17]. However, as the hemoglobin level rises in response, iron is transferred from storage tissues to the erythron (developing and mature red blood cells) and the patient continues to have ongoing losses of blood and iron related to the hemodialysis procedure [18]. As a result, after the initial increase in serum ferritin with intravenous iron treatment, both of these factors cause serum ferritin levels to decrease sharply, often returning back down to baseline [17]. In this study we found that for each g/dL increase in hemoglobin during an up hemoglobin excursion, that serum ferritin decreased by 82.2 ± 56.1 mg/dL. This relationship between iron and erythropoiesis is complicated further by the fact that as the hemoglobin level rises, the rHuEPO dose will often be decreased. So after the healthy initial effect of intravenous iron, with a robust increase in hemoglobin level, 1 to 3 months later the patient may again experience iron deficiency, but now while on a reduced dose of rHuEPO. A downward hemoglobin excursion will often result, explaining our observation of a complex relationship between intravenous iron dosing and hemoglobin cycling. In a sense, hemoglobin and iron cycling are two interwoven processes.

The impact of hemoglobin cycling on patients' health outcomes is not known. Under normal conditions of homeostasis, stable oxygen delivery to tissues is maintained by keeping the serum hemoglobin concentration fairly constant. Reduced oxygen delivery is sensed primarily through hypoxia-inducible factor-1 present in the kidney and other tissues [19]. When stimulated, this system leads to increased renal EPO production [20]. The bone marrow responds with increased production and survival of erythrocyte precursors which enter the circulation as reticulocytes [21]. This system maintains the hemoglobin concentration in response to challenges such as traumatic blood loss, menstruation, and hypoxia due to increased altitude. The frequent cycling of hemoglobin concentrations in hemodialysis patients treated with rHuEPO is an artificial phenomenon in the sense that it is not seen in normal healthy homeostasis. Hemoglobin fluctuations of this type may potentially cause pathologic tissue changes for a variety of reasons. In the heart, reduced hemoglobin concentration leads to left ventricular dilatation and hypertrophy [22]. This results at least in part from changes in intracardiac cellular growth signaling [23], although the mechanisms are incompletely understood. As hemoglobin levels rise and fall in hemodialysis patients, the disordered activation and resetting of cardiac growth signals could result in pathologic alterations in cardiac structure and function. Other tissues and organs throughout the body may also be sensitive to injury related to variability in hemoglobin level and oxygen delivery.

In addition to the potential organ damage induced by the heart's attempts to compensate for cycling hemoglobin levels, there may be pathology caused by wide fluxes of serum EPO levels resulting from repeated adjustments to rHuEPO doses due to cycling hemoglobin levels. While our best understanding of the effect of rHuEPO is its effect on bone marrow in the treatment of anemia, in recent years it has become clear that many tissues of the body have functioning cellular EPO receptors [24]. Cells in the brain [25], retina [26], heart [27], and kidneys [28] all are affected by EPO, receptor binding results in a cascade of signal transduction and gene activation. As a result, nonhomeostatic fluxes in serum EPO levels could potentially impact on the structure and function of each of these tissues.

Based on the findings from this study, potential strategies for the prevention of hemoglobin cycling emerge. A wider target hemoglobin range then the current 11 to 12 g/dL would reduce the need for frequent rHuEPO dose changes. Ideally, clinical performance measures and reimbursement policy should support such an approach by avoiding financial or other penalties for occasional hemoglobin results above or below the target range. It may be that less frequent measurement of hemoglobin level and the resulting rHuEPO dose adjustments would reduce the degree if cycling. Because of the contribution to hemoglobin cycling of intermittent intravenous iron treatment strategies, weekly maintenance intravenous iron dosing should be considered in appropriate patients to try to achieve "smoother" iron storage kinetics. In addition, research should be encouraged into EPO replacement strategies that more closely mimic native EPO physiology. Further research aimed at determining whether hemoglobin cycling occurs in other rHuEPO-treated populations such as patients with chronic kidney disease would be desirable.

CONCLUSION

We have found hemoglobin cycling to be a frequent finding in hemodialysis patients treated with rHuEPO.

The most important cause was frequent changes in rHuEPO dose, probably due in large part to the narrow hemoglobin target range. In addition, we found that patients with greater rHuEPO responsiveness tend to have a greater degree of hemoglobin cycling. Finally, there was a complex interaction between hemoglobin cycling and iron storage. Taken together these findings suggest that the current therapeutic paradigm of hemoglobin monitoring, iron treatment, and rHuEPO treatment results in recurrent nonphysiologic cycling of hemoglobin levels in hemodialysis patients.

Reprint requests to Steven Fishbane, M.D., 200 Old Country Road, Suite 135, Mineola, NY 11501.
E-mail:sfishbane@metrorenal.com

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