Check for updates

Erythroid Marrow Function in Anemic Patients

By Mario Cazzola, Pensri Pootrakul, Helmut A. Huebers, Mary Eng, Joseph Eschbach, and Clement A. Finch

Erythropoietic activity is known to be closely associated with marrow iron uptake. A modification of the standard measure of plasma iron turnover has been developed in which erythron transferrin uptake (ETU) rather than iron uptake has been calculated. The ETU has the advantage of providing a parameter of erythroid marrow activity independent of change produced by plasma iron and transferrin saturation. Measurements in 80 patients with anemia were compared to the normal value of 60 ± 12 μmol/L whole blood/d. The mean ETU for ten patients with severe aplastic anemia and for six patients with pure red-cell aplasia were 12 ± 8 and 12 ± 11 μmol/L whole blood/d, respectively. In ten transfusion-dependent patients with renal failure under dialysis therapy, the mean value was 35 ± 11, while ten other dialyzed patients who were transfusion independent had a mean ETU of 73 ± 21 μmol/L whole blood/d. Sixteen patients with hemolytic anemia had an average ETU of 400 ± 130, while 28 patients with ineffective erythropoiesis had a mean value of 474 ± 147 μmol/L whole blood/d. While patients with hypoproliferative anemia showed no relation between the severity of anemia and ETU, those with hyperproliferative erythroid marrow showed increasing values as the anemia became more severe. Sequential measurements in patients with aplastic anemia under treatment and in thalassemic patients under transfusion therapy showed the value of this measurement in monitoring the effects of treatment on erythroid marrow activity. It is concluded that the measurement of ETU provides a more direct ferrokinetic evaluation of erythroid activity in anemic states.

© 1987 by Grune & Stratton, Inc.

DISORDERS of erythroid marrow function may be characterized as affecting marrow proliferation and/or red cell maturation. For clinical purposes the former is evaluated by marrow aspiration or biopsy, and the latter by the relationship between the reticulocyte index and marrow proliferation as judged by marrow examination.[1] Limitations to the quantitation of erythroid marrow activity from a minute sample have led to a continued search for a more adequate means of estimating erythroid marrow activity. Beginning with the original measurements of Huff and associates,[2] the measurement of plasma iron turnover has been continually refined to reflect more quantitatively erythron iron uptake.[3–7]

In the last few years, attention has focused on the reaction between transferrin iron and its membrane receptors.[8,9] The assumption of a single plasma iron pool, so essential to previous kinetic measurements, has been shown to be erroneous.[10] There are actually two plasma iron pools, one composed of monoferric transferrin and the other of diferric transferrin. The diferric molecule has a greater capacity to deliver iron to tissue receptors than the monoferric species.[9,11] Since the in vivo loading of iron on transferrin is a random phenomenon, the quantitative relationship between these two plasma iron pools and their respective iron clearance is predictable.[10–12] The critical reaction is the uptake of the transferrin-iron-receptor complex into the cell, and this occurs at the same rate, regardless of whether there are one or two molecules of iron on the transferrin molecule. In a recent study dealing with normal subjects, a simple approach to the measurement of transferrin-receptor interaction in normal man was presented, and the transferrin uptake was shown to be independent of plasma iron concentration and transferrin saturation.[13] This approach has now been extended to the measurement of the erythron transferrin uptake in anemic patients.

MATERIALS AND METHODS

Patients. Ferrokinetic studies were performed in a total of 80 patients selected to provide extremes in erythropoiesis. A first group included ten individuals with severe aplastic anemia (AA) and six with pure red-cell aplasia (PRCA). Criteria for the diagnosis of severe aplastic anemia[14] included a hypocellular bone marrow on bone marrow biopsy (less than 30% cellularity) and two of the following three factors: reticulocyte index <1, granulocytes <0.5 × 10^9/L, and platelets <20 × 10^9/L.[14] Criteria for the diagnosis of PRCA[15] included the virtual absence of erythroid cells in the marrow but abundant marrow precursors for other cell species, a transfusion-dependent anemia associated with a decrease in reticulocyte index below 1, the presence of circulating granulocytes >2 × 10^9/L, and platelets >100 × 10^9/L. In addition to the above criteria and in order to select the most severely affected individuals, only those with less than or equal to 10% of injected radioiron in circulating red cells at two weeks were included in this first group. A second group was composed of 20 patients with severe renal disease with azotemia, all of whom were on renal dialysis. Within this group ten patients needed repeated transfusions to maintain their hematocrit over 20%, and ten other patients did not require transfusion.

The remaining 44 patients had anemia associated with erythroid marrow hyperplasia. There were 16 patients with hemolytic anemia, eight of whom had sickle cell disease, four hereditary spherocytosis, two red cell enzyme defects (pyruvate kinase deficiency, glucose 6-phosphate isomerase deficiency), one autoimmune hemolytic ane-

From the Department of Medicine, Divisions of Hematology and Kidney Diseases, University of Washington, Seattle, the Department of Internal Medicine and Medical Therapy, University of Pavia, Pavia, Italy, and the Thalassemia Center, Mahidol University, Bangkok, Thailand.

Submitted February 4, 1986; accepted August 13, 1986.

Supported in part by the National Institutes of Health Grant No. HL06242, CNR Progetto Finalizzato Oncologia, Grant No. 85.02084.44, USPHS Research Grant No. AM09805 from the National Institutes of Arthritis, Metabolism and Digestive Disease, and a grant from Associazione Italiana per la Ricerca sul Cancro.

The work reported in this paper was undertaken by Mario Cazzola during the tenure of Yamagiwa-Yoshida Memorial International Cancer Study Grant awarded by the International Union Against Cancer.

Address reprint requests to Dr Clement A. Finch, Providence Hospital, 4 East 500 17th Ave, Seattle, WA 98124.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "advertisement" *in accordance with 18 U.S.C. §1734 solely to indicate this fact.*

© 1987 by Grune & Stratton, Inc.

0006-4971/87/6901-0057$03.00/0

Downloaded from http://ashpublications.net/blood/article-pdf/69/1/296/596358/296.pdf by guest on 11 June 2024

mia, and one fragmentation hemolysis. Another group of 28 patients demonstrated ineffective erythropoiesis with erythroid marrow hyperplasia. Ten of these patients had β-thalassemia intermedia with hemoglobin concentrations between 6 and 9 g/dL,[16] while 16 patients had β-thalassemia/Hemoglobin E disease, the criteria for which have been described elsewhere.[17]

Ferrokinetic measurements. Details of the measurement of plasma iron turnover have been previously summarized.[18,19] In these studies it was standard practice to inject $^{59}FeSO_4$ (0.2 μg containing 2 μCi ^{59}Fe at pH 2) intravenously (IV) over a period of five minutes. However, in individuals with transferrin saturation >70%, radioiron was bound to normal plasma in vitro, and then the tracer saturation was adjusted to that of the patient's own plasma using cold ferrous ammonium sulfate.[13]

Plasma iron turnover was routinely calculated employing the formula[19]:

$$\text{PIT (mg/dL whole blood/d)} = \frac{\text{PI } (\mu g/dL) \times (100 - \text{Hct} \times 0.9)}{\text{T1/2 (min)} \times 100}$$

This formula is suitable for turnover measurements as long as the blood volume (BV) is not significantly different from that predicted (±10%). A comparison was made of the determined BV based on the dilution of the injected isotope, as compared to the predicted BV.[20] Where there was a significant increase (>10%), the observed PIT was corrected by multiplying it by the ratio between determined and predicted plasma volume for the patient's plasmatocrit.[19]

In some instances the radioiron red-cell utilization (RCU) was calculated from the red cell activity at 14 days and the amount of radioactivity injected as described by Cook and Finch.[19]

Additional calculations, discussed more in detail elsewhere,[13] were made to convert the plasma iron turnover to the transferrin-iron complex uptake by the erythron. This involved (a) the subtraction of the extravascular plasma flux (EVF), (b) a correction designed to convert tissue iron uptake (IU) to tissue transferrin uptake (TU), and (c) the subtraction of nonerythroid transferrin uptake to leave erythron transferrin uptake (ETU).

$$\text{EVF (mg/dL wb/d)} = \text{PI } (\mu g/dL) \times \frac{(100 - \text{Hct} \times 0.9)}{100} \times 0.0015$$

$$\text{IU (mg/dL wb/d)} = \text{PIT} - \text{EVF}$$

$$\text{TU } (\mu mol/L\,wb/d) = \frac{\text{IU (mg/dL wb/d)} \times 10{,}000}{56} \times \frac{200 + 2.2S}{200 + 6.4S}$$

where S is the percent transferrin saturation, and wb/d stands for whole blood/day.

The final correction to allow for transferrin-iron going to nonerythroid receptors is made by subtracting the mean volume value of 11 μmol/L whole blood/day[13] from the calculated transferrin uptake:

$$\text{ETU } (\mu mol/L\,wb/d) = \text{TU } (\mu mol/L\,wb/d) - 11$$

Plasma iron and transferrin saturation were measured as described elsewhere.[21,22] Hematocrit was determined by the micromethod. ^{59}Fe activity was determined by gamma counting. Plasma volume was calculated from the ^{59}Fe-transferrin dilution.[19]

Statistical analysis. Statistical analysis was performed using the CLINFO computer system (University of Washington, Seattle, WA). All results are given as mean ±1 SD. The significance of the differences between means was tested by the Student's *t* test.

RESULTS

Data obtained in 80 subjects are summarized in Table 1. Ten patients with aplastic anemia had an average transferrin saturation of 90% ± 9%, a mean plasma iron turnover of 0.57 ± 0.10 mg/dL whole blood/d, and a mean ETU of 12 ± 8 μmol/L whole blood/d. Radioactivity in the blood at two weeks amounted to an average of 4% ± 4% (range 0% to 10%). Six additional patients with PRCA had a mean transferrin saturation of 94% ± 5%, a mean plasma iron turnover of 0.57 ± 0.15 mg/dL whole blood/d, an ETU of 12 ± 11 μmol/L whole blood/d, and a mean red-cell utilization at two weeks of 3% ± 3% (range 0% to 6%). Thus, in these subjects the mean values for PIT were 80% of normal whereas ETU values averaged 20% of normal.

Ten patients with transfusion-dependent renal failure under continuous dialysis treatment had a mean transferrin saturation of 80% ± 15%, a mean plasma iron turnover of 0.73 ± 0.16 mg/dL whole blood/d, and an average ETU of 35 ± 11 μmol/L whole blood/d. Red cell utilization in the ten patients averaged 26% ± 10% (range 12% to 47%). By contrast, a second group of dialyzed patients who were able to sustain their hematocrit without transfusion had a mean transferrin saturation of 28% ± 6%, a mean PIT of 0.77% ± 18% mg/dL whole blood/d, and a mean ETU of 73 ± 21 mmol/L whole blood/d. Their red cell utilization averaged 71% ± 13% (range 55% to 89%). Whereas there was no difference between the mean PITs of the two groups of renal patients ($t = 0.55$, $P > 0.05$), the mean ETU of those patients who did not need blood transfusions was significantly higher than that of transfusion-dependent patients ($t = 5.17$, $P < 0.0001$).

Sixteen patients with hemolytic anemia were heterogeneous in respect to the cause of their anemia, to its degree (hematocrit varied from 18% to 35.5%), plasma iron concentration (46 to 279 μg/dL), and transferrin saturation (11% to 91%). Plasma iron turnover averaged 3.86 ± 1.45 mg/dL whole blood/d but ranged from 1.26 to 6.64 mg/dL whole blood/d. ETU averaged 400 ± 130 μmol/L whole blood/d but ranged from 168 to 612 μmol/L whole blood/d.

A similar heterogeneity was observed in 28 patients with ineffective erythropoiesis. Hematocrits varied from 15.1% to 34.5%, plasma iron from 52 to 308 μg/dL, and transferrin saturation from 16% to 98%. Mean PIT was 5.11 ± 1.85 mg/dL whole blood/d with a range from 1.40 to 9.23, and ETU values averaged 474 ± 147 μmol/L whole blood/d with a range from 176 to 809.

All patients with aplastic anemia, pure red-cell aplasia, and renal failure associated with anemia had erythroid marrow activity as judged by ETU between 0 and 1.6 × basal. On the other hand, patients with hemolytic anemia and ineffective erythropoiesis showed values between 2.8 and 13.5 times basal (all values but two being greater than 3). When ETU was plotted against the hematocrit (Fig 1), there was no apparent relationship among hypoproliferative patients between the severity of the anemia and ETU (r = 0.32, $P = 0.06$), whereas there was an inverse correlation among hyperproliferative patients (r = −0.71, $P < 0.001$).

Sequential studies were carried out in five patients with pure red-cell aplasia under treatment after an appropriate interval of time (Fig 2). These measurements showed no change in marrow activity in two patients and improvement in three by both improvement in hematocrit and clearly

Downloaded from http://ashpublications.net/blood/article-pdf/69/1/296/596358/296.pdf by guest on 11 June 2024

Table 1. Ferrokinetic Studies

Condition	Hct (%)	Retic Index (× basal)	Plasma Iron (μg/dL)	Tf Sat. (%)	T-1/2 (min.)	RCU (%)	PIT (mg/dL/d)	ETU (μmol/L/d)
Normal Subjects (53)	42 ± 4	~1	112 ± 43	35 ± 11	80 ± 15	85 ± 4	0.71 ± 0.17	60 ± 12
Aplastic Anemia (10)	30	0.3	493	98	530	6	0.68	1
	22	0.0	319	96	415	0	0.62	10
	22	0.0	154	87	292	—	0.42	11
	13	0.5	189	80	272	—	0.61	23
	31	0.1	350	94	426	—	0.59	8
	24	0.3	197	69	404	0	0.38	4
	17	0.3	243	95	307	2	0.67	21
	17	0.1	282	95	464	0	0.51	3
	27	0.1	282	96	345	10	0.62	16
	25	0.1	228	90	307	8	0.57	17
Average:	23 ± 6	0.2 ± 0.2	274 ± 9	90 ± 9	376 ± 88	4 ± 4	0.57 ± 0.10	12 ± 8
Pure Red-Cell Aplasia (6)	14	0.0	202	85	399	6	0.44	6
	16	0.0	274	97	331	1	0.71	21
	27	0.2	300	94	245	—	0.77	28
	20	0.1	322	98	456	5	0.58	5
	29	0.0	178	94	275	—	0.47	14
	20	0.0	244	96	472	0	0.42	0
Average:	21 ± 6	0.1 ± 0.1	253 ± 56	94 ± 5	363 ± 94	3 ± 3	0.57 ± 0.15	12 ± 11
Renal Failure A (10)	28	1.2	146	50	206	47	0.53	28
	26	0.6	205	78	234	16	0.67	30
	22	0.8	217	82	249	33	0.70	30
	23	1.0	196	81	192	17	0.70	33
	26	1.0	261	89	202	23	0.99	52
	20	1.9	275	93	240	24	0.94	44
	20	2.4	181	85	222	32	0.67	31
	22	0.9	206	92	374	12	0.55	17
	18	1.6	187	88	177	33	0.88	48
	22	0.4	184	57	222	27	0.67	35
Average:	23 ± 3	1.2 ± 0.6	206 ± 38	80 ± 15	232 ± 55	26 ± 10	0.73 ± 0.16	35 ± 11
Renal Failure B (10)	29	1.6	82	30	70	85	0.87	83
	28	0.9	57	21	53	89	0.80	86
	31	1.4	76	28	94	71	0.58	50
	20	0.4	67	31	120	66	0.46	34
	24	2.0	135	41	114	62	0.93	75
	30	1.1	78	23	62	89	0.92	97
	16	2.8	56	22	84	57	0.57	54
	29	1.9	61	24	66	75	0.69	68
	20	0.8	84	34	76	55	0.91	84
	31	1.8	98	30	72	64	0.99	96
Average:	26 ± 5	1.5 ± 0.7	79 ± 24	28 ± 6	81 ± 22	71 ± 13	0.77 ± 0.18	73 ± 21
Hemolytic Anemia (16)	30	—	130	44	32	—	2.98	301
	24	—	72	30	19	—	3.74	432
	30	—	109	34	39	—	2.76	295
	26	9.0	148	60	25	66	4.56	435
	21	—	97	35	28	—	5.09	558
	21	—	104	38	23	—	5.65	612
	24	—	107	38	23	49	4.45	480
	22	—	279	91	34	—	6.64	545
	28	—	77	27	26	—	2.22	254
	32	—	254	81	32	—	5.52	482
	25	4.2	55	17	15	87	2.93	382
	32	—	46	11	26	95	1.26	168
	27	6.6	88	33	17	—	3.99	450
	34	4.2	133	40	44	—	2.09	209
	36	4.4	234	86	40	63	3.98	335
	18	6.0	78	34	17	—	3.89	435
Average:	27 ± 5	5.7 ± 1.9	126 ± 70	44 ± 24	27 ± 9	72 ± 19	3.86 ± 1.45	400 ± 130

Downloaded from http://ashpublications.net/blood/article-pdf/69/1/296/596358/296.pdf by guest on 11 June 2024

Table 1. Ferrokinetic Studies (Cont'd)

Condition	Hct (%)	Retic Index (x basal)	Plasma Iron (μg/dL)	Tf Sat. (%)	T-1/2 (min.)	RCU (%)	PIT (mg/dL/d)	ETU (μmol/L/d)
Ineffective Erythropoiesis (28)	30	0.3	52	16	29	42	1.40	176
	27	0.3	94	35	21	28	3.38	371
	25	2.1	85	37	16	29	4.67	515
	22	0.8	80	39	25	41	4.55	486
	25	—	133	90	17	14	5.99	523
	23	—	128	86	25	19	6.24	545
	21	0.3	308	97	63	33	4.92	389
	20	1.4	73	35	13	22	5.63	635
	31	0.8	95	43	25	43	3.32	345
	24	—	60	34	14	23	3.86	434
	32	0.5	80	34	36	—	2.15	228
	15	—	134	91	18	9	9.23	809
	25	—	246	97	31	42	5.46	454
	19	—	241	93	37	28	6.56	551
	21	—	185	94	22	28	8.80	760
	20	—	280	85	40	44	8.44	726
	23	—	179	97	26	—	6.78	575
	18	—	243	98	47	—	5.53	450
	24	0.8	192	71	30	—	5.01	454
	25	1.2	137	59	24	—	4.45	426
	21	1.0	140	67	25	—	4.65	430
	30	0.8	138	49	30	—	3.37	336
	35	1.0	150	50	28	—	3.69	365
	31	0.5	139	51	23	—	4.36	435
	24	1.2	224	74	41	—	4.28	375
	24	1.4	207	74	23	—	7.03	642
	31	0.7	174	78	23	—	5.43	487
	31	1.2	179	67	33	—	3.93	358
Average:	25 ± 5	0.9 ± 0.5	156 ± 68	66 ± 25	28 ± 11	30 ± 11	5.11 ± 1.85	474 ± 147

demonstrable increases in marrow erythroid activity. Sequential measurements in patients with thalassemia or sickle cell anemia undergoing transfusion therapy showed the suppressive effect of higher hematocrit on erythroid activity but erythropoietic activity was still two to three times basal for hematocrit values around 40% (Fig 3). In these latter studies there was a close correlation ($r = 0.86$, $P <$ 0.01) between ETU and erythroid: myeloid ratio of the marrow.

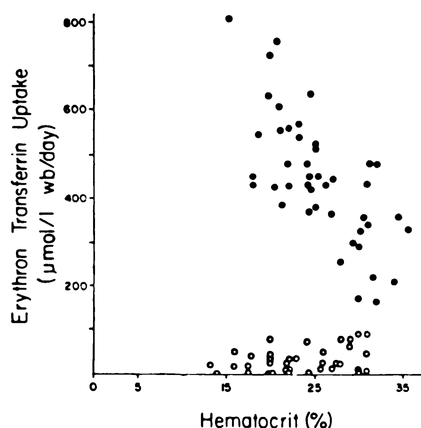

Fig 1. Relationship between hematocrit and erythron transferrin uptake (ETU) in anemic patients. Patients with conditions known to be associated with impaired proliferative response to anemia are shown with open circles (○) and patients with conditions associated with a normal proliferative response to anemia are shown with solid circles (●).

DISCUSSION

Within the circulating blood there is a constant flow of iron from donating cells via transferrin to membrane transferrin receptors of tissues requiring iron. The marrow normally receives about four fifths of all iron passing through

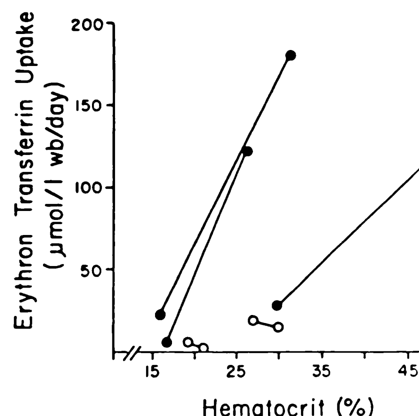

Fig 2. Ferrokinetic studies carried out before and after treatment in patients with pure red cell aplasia. Three patients showed both improvement in hematocrit and increased marrow erythroid activity, while two unresponsive patients showed no change in either.

Downloaded from http://ashpublications.net/blood/article-pdf/69/1/296/596358/296.pdf by guest on 11 June 2024

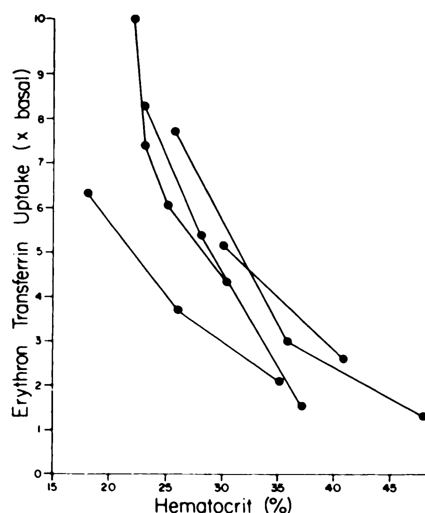

Fig 3. Sequential ferrokinetic studies in patients with thalassemia and sickle cell anemia undergoing transfusion therapy. The relationship between hematocrit concentration and erythropoietic activity is illustrated.

the plasma for incorporation into hemoglobin. It has therefore been assumed that erythroid marrow function would be quantitatively related to iron turnover. In some conditions, however, the plasma iron turnover gives a poor reflection of the state of erythropoiesis, since other pathways of iron exchange are increased while erythron iron uptake is reduced. A number of elegant models of iron kinetics have been developed that take into consideration the amount of iron going to erythroid and nonerythroid tissues and various refluxes of iron from those tissues.[4,6,7] Such models require sophisticated processing of experimental data derived from blood sampling over ten to 14 days, and although they have been of value in developing an understanding of erythroid disorders, they are not practical for clinical usage and the results are themselves subject to criticism. These models are based on the erroneous assumption of a single plasma iron pool and, for the most part, have not considered the effect of transferrin saturation on iron turnover. The principal focus of this work was to develop a simple ferrokinetic approach to quantitation of erythropoiesis by applying recent knowledge concerning iron exchange between transferrin and body cells to ferrokinetic measurements.

The plasma iron turnover is derived from the hematocrit, the plasma iron, and the rate of disappearance of radioiron from circulation.[18,19] Before a relationship between iron turnover and erythropoietic activity could be exploited, it was first necessary to allow for transferrin iron going to extravascular fluid and not initially taken up by cells. This was done based on the relationship previously described by Cook et al between plasma iron and extravascular flux.[4]

The key to the present approach depends on the reaction between transferrin iron and its membrane receptors. We have previously shown that the plasma iron turnover increases with increasing plasma iron and transferrin saturation.[13] Cook et al[4] thought this was due to increased nonerythroid iron uptake, an assumption no longer tenable. It is now known to be due to an increased proportion of diferric iron as saturation increases and the greater capacity of diferric transferrin to deliver iron to all membrane receptors, erythroid and nonerythroid. This does not necessarily imply that erythropoiesis is increased at higher saturations but is rather a reflection of the increased proportion of diferric transferrin molecules.

We have demonstrated that transferrin uptake can be derived empirically from plasma iron turnover, once extravascular flux has been subtracted, knowing the preference ratio between the two forms of plasma iron and the relative amount of each.[13] Transferrin uptake so derived was found to be independent of plasma iron and transferrin saturation, and this suggested that the critical measurement of erythroid marrow function could be best described by erythroid transferrin uptake once allowance had been made for nonerythroid transferrin uptake. The nonerythroid tissues of the body have a limited capacity to assimilate iron. After injection of radioiron, normal subjects have only about 15% of the activity outside of the red cell mass at two weeks. Furthermore, there is little evidence to date that these nonerythroid receptors, most of which reside in the liver, can change greatly in number except in the presence of iron deficiency (Tanin et al, unpublished data). This means that the number of iron-bearing transferrin molecules reacting with membrane receptors on nonerythroid tissues can be considered relatively constant, and the mean normal value of 11 μmol transferrin/L whole blood/d has been assumed in the present study.[13] According to these calculations, erythron transferrin uptake in normal subjects averages 60 ± 13 μmol/L whole blood/d.

A first opportunity to examine the appropriateness of the various corrections made to obtain the ETU was provided by patients with severe aplastic anemia and pure red-cell aplasia. Among the 16 patients studied, whose plasma iron turnover ranged from 0.38 to 0.77 mg/dL whole blood/d, values for ETU ranged from 0 to 28 μmol/L whole blood/d. No patient had a value below 0, indicating that estimates of nonerythroid iron turnover were not overcorrected. The red cell utilization of 3% to 4% when compared to the mean ETU of 12% the basal value suggested that a major portion of the residual erythroid activity in these patients did not result in the production of viable red cells. Evidence of dyspoiesis in aplastic anemia has been reported.[23,24]

Studies in renal patients provided another opportunity to compare the clinical status with the ferrokinetic evaluation of erythropoiesis. Renal patients have a combination of impaired marrow stimulation due primarily to inadequate erythropoietin production and also increased red cell hemolysis, but erythropoiesis is effective.[18] Studies of two groups of dialyzed patients, one self-sufficient and the other transfusion dependent, showed no difference in plasma iron turnover (0.77 ± 0.18 *v* 0.73 ± 0.16 mg/dL whole blood/d) but a conspicuous difference in erythroid activity in the two groups, ie, 73 ± 21 *v* 35 ± 11 μmol/L whole blood/d. Assuming that both had the same degree of shortening of red cell life span to about one-half normal, the difference in hemoglobin concentration was adequately explained by the greater impairment in production in the transfused group.

Patients with hemolytic anemia had an average ETU of 400 ± 130, and patients with ineffective erythropoiesis 474 ±

Downloaded from http://ashpublications.net/blood/article-pdf/69/1/296/596358/296.pdf by guest on 11 June 2024

147 μmol/L whole blood/d. These can be translated into mean erythropoietic rates of 6.7 and 7.9 times basal, respectively. In some of these patients the reduction of erythropoiesis after transfusion was measured (Fig 3). Quantitative aspects of the relationship between blood hemoglobin concentration or hematocrit and suppression of erythropoiesis are not well defined. There is ample clinical evidence that suppression of erythropoiesis by transfusion is required for thalassemic patients if distension of the marrow and distortion of the skeleton are to be prevented. Previous measurements on patients with thalassemia were made by Cavill et al[25] at hemoglobin levels from 9 to 17 g/dL. According to their detailed analysis of the plasma iron disappearance curve, erythropoiesis as judged by marrow iron turnover became normal or subnormal at a blood hemoglobin concentration of 11 to 12 g/dL. They comment, however, that the marrow still showed normoblastic hyperplasia. It might be anticipated from the type of analysis performed by them that ineffective erythropoiesis could not be completely separated from iron exchange with nonerythroid tissues, and this could cause total erythropoiesis to be underestimated.[18,26] In studies reported here, erythropoiesis did decrease as the hemoglobin concentration was increased by transfusion but remained two to three times basal at a hemoglobin concentration of 11 to 12 g/dL, and parallel changes in erythroid: myeloid ratio validated the ferrokinetic measurement. Evaluation of erythroid activity can be of value in determining the degree of erythroid suppression after transfusion in individual patients with thalassemia major and also in deciding whether patients with thalassemia intermedia should be transfused.

Taken as a group, individuals with an impaired marrow response to anemia, ie, less than two times basal, showed no relationship between the ETU and hematocrit, the slope of the regression line being not significantly different from 0. This suggested that the impairment in production was the dominant feature in causing the anemia and that the erythroid marrow could not respond appropriately to the erythropoietin stimulus produced by anemia. In contrast, patients with an appropriate proliferation response to anemia showed an inverse relationship between hemoglobin concentration and erythropoietic response. This would be consistent with an increased marrow stimulation by erythropoietin as the hemoglobin fell.[1] A similar relationship has been observed employing a more complex ferrokinetic approach.[27]

REFERENCES

1. Finch CA: Erythropoiesis, erythropoietin, and iron. Blood 60:1241, 1982

2. Huff RL, Hennessy TG, Austin RE, Garcia JF, Roberts BM, Lawrence JH: Plasma and red cell iron turnover in normal subjects and in patients having various hemopoietic disorders. J Clin Invest 29:1041, 1950

3. Pollycove M, Mortimer R: The quantitative determination of iron kinetics and hemoglobin synthesis in human subjects. J Clin Invest 40:753, 1961

4. Cook JD, Marsaglia G, Eschbach JW, Funk DD, Finch CA: Ferrokinetics: A biological model for plasma iron exchange in man. J Clin Invest 49:197, 1970

5. Finch CA, Deubelbeiss K, Cook JD, Eschbach JW, Harker LA, Funk DD, Marsaglia G, Hillman RS, Slichter S, Adamson JW, Ganzoni A, Giblett ER: Ferrokinetics in man. J Clin Invest 43:17, 1970

6. Cavill I, Ricketts C: Human iron kinetics, in Jacobs A, Worwood M (eds): Iron in Biochemistry and Medicine, II. London, Academic Press, 1980, p 573

7. Stefanelli M, Barosi G, Cazzola M: Iron kinetics, in Cramp DG (ed): Quantitative Approaches to Metabolism. Chichester, England, Wiley, 1982, p 143

8. Huebers HA, Josephson B, Huebers E, Csiba E, Finch CA: Uptake and release of iron from human transferrin. Proc Natl Acad Sci USA 78:2572, 1981

9. Huebers HA, Csiba E, Huebers E, Finch CA: Competitive advantage of diferric transferrin in delivering iron to reticulocytes. Proc Natl Acad Sci USA 80:300, 1983

10. Huebers HA, Uvelli D, Celada A, Josephson B, Finch CA: Basis of plasma iron exchange in the rabbit. J Clin Invest 70:763, 1982

11. Huebers HA, Csiba E, Huebers E, Finch CA: Molecular advantage of diferric transferrin in delivering iron to reticulocytes: A comparative study. Proc Exp Biol Med 179:222, 1985

12. Huebers HA, Josephson B, Huebers E, Csiba E, Finch CA: Occupancy of the iron binding sites of human transferrin. Proc Natl Acad Sci USA 81:4326, 1984

13. Cazzola M, Huebers HA, Sayers MH, MacPhail P, Eng M, Finch CA: Transferrin saturation plasma iron turnover and transferrin uptake in normal man. Blood 66:935, 1985

14. Camitta BM, Thomas ED, Nathan DG, Santos G, Gordon-Smith EC, Gale RP, Rappaport JM, Storb R: Severe aplastic anemia: A prospective study of the effect of early marrow transplantation on acute mortality. Blood 48:63, 1976

15. Krantz SB: Pure red cell aplasia. N Engl J Med 291:345, 1974

16. Weatherall DJ, Clegg JB: The Thalassemia Syndromes, ed 3. Oxford, Blackwell, 1981

17. Pootrakul P, Hungsprenges S, Fucharoen S, Baylink D, Thompson E, English E, Lee M, Burnell J, Finch CA: Relation between erythropoiesis and bone metabolism in thalassemia. N Engl J Med 304:1470, 1981

18. Bothwell TH, Charlton RW, Cook JD, Finch CA: Iron Metabolism in Man. Oxford, Blackwell, 1979

19. Cook JD, Finch CA: Ferrokinetic measurements, in Cook JD (ed): Iron. New York, Churchill Livingstone, 1980, p 134

20. Nadler SB, Hidalgo, Bloch T: Prediction of blood volume in normal human adults. Surgery 51:224, 1962

21. ICSH Expert Panel on Iron. Recommended methods for measurement of serum iron in human blood. Br J Haematol 38:291, 1978

22. ICSH Expert Panel on Iron: The measurement of total and unsaturated iron binding capacity in serum. Br J Haematol 38:281, 1978

23. Frisch B, Lewis SM, Sherman D: The ultrastructure of dyserythropoiesis in aplastic anemia. Br J Haematol 29:545, 1975

24. Lewis SM: Dyserythropoiesis in aplastic anaemia, in Geary CG (ed): Aplastic Anaemia. London, Bailliere Tindall, 1979, p 82

25. Cavill I, Ricketts C, Jacobs A, Letsky E: Erythropoiesis and the effect of transfusion in homozygous β-thalassemia. N Engl J Med 298:776, 1978

26. Bell R, Orr JS: Ferrokinetic analysis of clearance curves. Br J Haematol 45:165, 1980

27. Barosi G, Cazzola M, Berzuini C, Quaglini S, Stefanelli M: Classification of anemia of the basis of ferrokinetic parameters. Br J Haematol 61:357, 1985

Downloaded from http://ashpublications.net/blood/article-pdf/69/1/296/596358/296.pdf by guest on 11 June 2024