Problems in Ferrokinetics: extra radio-iron fixation to red cells

Hiroshi Saito

Department of Internal Medicine, Kawamura Hospital, 1-84 Daihannya, Akutami, Gifu, Japan

ABSTRACT

Red cell radio-iron utilization (RCU) exceeds the ratio red cell iron per whole-body iron due to the extra red cell fixation of radio-iron refluxed from tissue. The extra red cell radio-iron fixation reduces the radio-iron distribution to non-erythron tissue. Affected by RCU, the red cell iron turnover rate (RCIT) becomes larger than the net red cell iron turnover rate, which is indicated by the red cell iron renewal rate (RCIR). To clarify the influences of such biased radio-iron distributions, the values assayed by ferrokinetics were compared with those assayed by the methods other than ferrokinetics. The results showed the underestimation of the tissue and storage iron turnover rates in all cases determined using RCIT by ferrokinetics. All the previous investigators of ferrokinetics probably misunderstood the excess of RCIT as an iron turnover rate of the reflux from a labile iron pool in erythroblasts in normal subjects. However, such a reflux from erythroblasts is unlikely to exist in normal subjects with rapid and effective erythropoiesis. Influences on the iron turnover rates by the extra radio-iron distribution to red cell mass in iron deficiency anemia and by the radio-iron fixation to storage in hereditary hemochromatosis were also discussed from a new perspective.

Keywords: ferro-erythrokinetics, biased radio-iron distribution to red cells, Biased radio-iron distribution to tissue, Tissue iron turnover rate, Storage iron turnover rate

INTRODUCTION

Plasma iron mediates iron turnover in the body. Plasma radio-iron taken up by red cell precursors (erythroblasts and reticulocytes) is fixed to red cells for their whole life. At the ending of red cell life, senescent red cells are captured and digested by reticuloendothelial phagocytes (macrophages).

Most body iron recycles for erythropoiesis. On the other hand, a smaller amount of iron turns over between plasma and non-erythron tissue iron components. The storage iron turnover is the major one among the non-erythron tissue iron turnover.

The noticeable advances in the studies on the erythropoiesis and non-erythron tissue iron turnovers are as follows:

In 1950, ferrokinetics was developed by Huff et al.\(^1,2\) It was an epoch-making contribution to the studies on clinical hematology.
In 1961, Pollycove M, et al. analyzed the plasma radio-iron disappearance curve for the quantitative determination of hemoglobin synthesis and iron turnover of other iron components. Thereafter, many investigators such as Finch CA, et al., Hosain F, et al., Cook JD, et al., Ricketts C, et al. and others reexamined the ferrokinetics and proposed various versions. However, all the previous investigators disregarded the influence of extra radio-iron fixation to red cell mass and the resultant reduction of radio-iron distribution to non-erythron tissue cells in ferrokinetics.

The author attempted to elucidate such problems before and here further by comparing the values determined by ferrokinetics with those determined by the methods other than ferrokinetics.

METHOD

1) Materials
Ferrokinetics data:
   Previous ferrokinetics data of normal subjects were used.
   Radio-iron was used for the determination of iron loss in excreta in normal subjects.

The data about the cell storage iron and the cell life span of normal subjects:
   Three kinds of major iron-storing cells (macrophage, hepatocyte and enterocyte) were used for determining the sum of storage iron turnover rates in normal subjects. These data cited from various sources are referred to the sources at the citation sites in the paper.
Radio-iron distribution bias causes errors in determining the body iron turnover by ferrokinetics

2) Methods

Plasma iron turnover rate (PIT):

PIT is an index of the whole-body iron turnover rate. However, the majority of PIT represents the iron turnover by erythropoiesis. PIT other than erythropoiesis is the iron turnover rates of tissue iron components; iron stores, myoglobin and enzymes.

The plasma iron half disappearance rate (PID) t1/2 is determined from the initial radio-iron decrease curve. Plasma radio-iron decreases, rapidly extracted by pre-existing body iron components.

\[
PIT \text{ mg/day} = \frac{0.693 \times PI \text{ (mg/l)} \times PV \text{ (ml)} \times 24}{PIDt1/2}
\]

Red cell radio-iron utilization (RCU):

RCU is the percent ratio of radio-iron incorporated in circulating red cells within 2 weeks per total radio-iron injected.

RCU is composed of the early and delayed radio-iron uptake by red cell precursors from plasma radio-iron. The delayed red cell radio-iron uptake means the additional red cell fixation of radio-iron refluxed from tissue. Thus, RCU becomes larger than the ratio pre-existing red cell iron (RCI) per whole-body iron (WBI) and indicates the extra of radio-iron distribution (fixation) to red cells.

\[
RCU/100 = \frac{(\text{Red cell } ^{59}\text{Fe after 2 weeks})}{(\text{Total } ^{59}\text{Fe injected})}
\]

Red cell iron turnover rate (RCIT):

RCIT is obtained by multiplying red cell radio-iron utilization (RCU)/100 by PIT together. Therefore, RCIT affected by RCU exceeds the net red cell iron turnover rate.

The erythrocyte iron turnover rate (EIT) is a synonym of RCIT.

\[
RCIT \text{ ( = EIT) } = PIT \times RCU/100
\]

Red cell iron renewal rate (RCIR):

RCIR, an index of effective erythropoiesis by erythrokinetics. It indicates the net red cell iron turnover rate.

RCIR is obtained by dividing the red cell iron (RCI) by the mean red cell life span (MRCLS) determined by DF32P, which labels whole red cell generations. MRCLS can also be determined roughly from a dip in the red cell radio-iron utilization curve following longer than 120 days after radio-iron injection in normal subjects.

\[
RCIR = \frac{RCI}{MRCLS \text{ by DF32P}}
\]

The difference between RCIT and RCIR indicates the excess of radio-iron fixation to red cell mass.

Non-RCIR is obtained by subtracting RCIR from PIT.

\[
\text{Non-RCIR} = (\text{PIT} - \text{RCIR})
\]

Non-RCIR, PIT – RCIR, indicates the net non-red cell tissue iron turnover rate (TIT) in normal subjects.

\[
\text{TIT in normal subjects.}
\]

TIT includes the iron turnover rate of myoglobin and enzymes. It also includes the iron
turnover rate by ineffective erythropoiesis in some disease states.

\[ \text{Non-RCIT (PIT – RCIR)} = \text{TIT \pm Iron turnover rate of ineffective erythropoiesis}. \]

TIT is composed of the storage iron turnover rate (SIT) and non-storage iron turnover rate (Non-SIT). Non-SIT is composed of the iron turnover rates of myoglobin and enzymes.

\[ \text{TIT = Non-RCIR} = \text{SIT} + \text{Non-SIT} \]

The storage iron turnover rate (SIT) is determined by dividing the cell storage iron by the mean cell life span, as the sum of the storage iron turnover rates of the 3 major iron-storing cells (macrophage, hepatocyte and enterocyte).

\[ \text{Storage iron turnover rate (SIT)} = \frac{\text{Cell storage iron}}{\text{Mean cell life span}} \]

The sum of the storage iron turnover rates of the 3 major iron-storing cells is regarded to approximate the total storage iron turnover rate (SIT).

SIT can be determined from TIT, if the ratio SIT/TIT is known. Although the ratio SIT/TIT is around 0.6 in normal subjects, it is variable individually.

RESULTS

1) Body iron turnover rates in a normal model

The standard normal model was selected as follows: body weight 70 kg,\(^{1,3,6,9}\) WBI 3.6 g, RCI 2.4 g, non-red cell tissue iron 1.2 g and storage iron 0.6 to 1.0 g.\(^{10}\) From the above-described model, the iron turnover rates of body iron components were estimated and shown in Fig. 2. Fig. 2 is cited from Fig. 7 in reference\(^{11}\) after a slight modification.

2) Storage iron turnover rate not determined by ferrokinetics

Macrophage in spleen receives 20 mg/day of red cell iron from red cell mass, and it releases the same amount of iron to plasma in equilibrium in normal subjects. Therefore, the 20 mg/day of RCIR, the net red cell iron turnover rate, indicates the macrophage iron turnover rate, but not the macrophage storage iron turnover rate.

The average macrophage storage iron turnover rate was calculated by dividing the macrophage storage iron 500 mg; the average of 400 to 600 mg,\(^{10}\) by the macrophage life span 105 days; the average of 3 to 4 months.\(^{12}\) Then, the average macrophage storage iron turnover rate became 4.8 mg/day.

The average storage iron turnover rate of hepatocyte was calculated by dividing the hepatocyte storage iron 267 mg; the average of 200 to 333 mg,\(^{10}\) by the hepatocyte life span 400 days; the average of 300 to 500 days.\(^{13,16}\) Then, the average hepatocyte storage iron turnover rate became 0.7 mg/day. The marrow storage iron turnover rate was obtained by dividing the bone marrow macrophage storage iron 288 mg\(^{10}\) by the mean macrophage life span 105 days.\(^{10}\) Then, the average marrow macrophage storage iron turnover rate became 2.8 mg/day.

Iron absorption is around 1 mg/day in normal male subjects. Therefore, 1 mg/day iron absorption indicates the enterocyte iron turnover (pass) rate, but not the enterocyte storage iron turnover rate.

The enterocyte storage iron turnover rate was determined from the cumulative radio-iron loss in stool.\(^9\) The radio-iron appeared in stool by the exfoliation of enterocytes within 10 days was 0.66% and 0.45% in 2 normal male subjects (average 0.55%); where 10 days was the duration of radio-iron appearing in stool by epithelial exfoliation in 2 weeks. Then, the average enterocyte storage iron turnover rate in the normal subjects was calculated as follows: PIT (30 mg/day) \(\times (0.55/100) = 0.17\) mg/day. The thus obtained enterocyte iron turnover rate was corrected by dividing 0.17 mg/day by the radio-iron distribution reduction ratio 0.6, which was derived from
Radio-iron distribution bias causes errors in determining the body iron turnover by ferrokinetics.

The formula: correction coefficient = \{1 – (RCU/100)\}/\{1 – (RCIR/PIT)\} = (1 – 0.8)/(1 – 0.67) = 0.20/0.33 = 0.6. Then, the corrected enterocyte storage iron turnover rate became 0.3 mg/day, which corresponded to 1/3 of the whole-body iron loss rate 1 mg/day.9,15-17

The sum of the storage iron turnover rates of the 3 major iron-storing cells became 5.8 mg/day; macrophage (4.8 mg/day), hepatocyte (0.7 mg/day) and enterocyte (0.3 mg/day). Therefore, the value 5.8 mg/day was considered to be the standard SIT approximate to the total storage iron turnover rate in normal subjects. The value 5.8 mg/day corresponds to 19% of the whole-body iron turnover rate (PIT 30 mg/day).

The macrophage storage iron turnover rate was 7 times higher than the hepatocyte storage iron turnover rate.

Fig. 2 Iron turnover rates in a normal model.
The pink area at the center indicates the 360° proportion of the plasma iron turnover rate (PIT).
The blue area indicates the 288° proportion of the red cell iron turnover rate (RCIT) at 80% radio-iron utilization (RCU).
The green area indicates the 240° proportion of the red cell iron renewal rate (RCIR); the net red cell iron turnover rate.
The tissue iron turnover rate (TIT); (PIT – RCIR) accounts for the 120° proportion as the sum of the red area (SIT) and purple area (Non-SIT).
The TIT is composed of the two kinds of tissue iron turnover rates; the TIT due to the radio-iron fixed to tissue iron components (TITf), and the TIT due to the radio-iron released from tissue iron components to plasma (TITr) within 2 weeks.
The yellow area indicates the 72° proportion of TITr.
The blue area extruding from the area-angle of RCIR into the area-angle of TIT indicates the 48° proportion of TITr at 80% red cell radio-iron utilization (RCU).
The blue area indicates the 288° proportion of the red cell iron turnover rate (RCIT).
The green area indicates the 240° proportion of the red cell iron renewal rate (RCIR). The tissue iron turnover rate (TIT); (PIT – RCIR) accounts for the 120° proportion as the sum of the red area (SIT) and purple area (Non-SIT).
The TIT is composed of the two kinds of tissue iron turnover rates; the TIT due to the radio-iron fixed to tissue iron components (TITf), and the TIT due to the radio-iron released from tissue iron components to plasma (TITr) within 2 weeks.
The yellow area indicates the 72° proportion of TITr.
The blue area extruding from the area-angle of RCIR into the area-angle of TIT indicates the 48° proportion of TITr at 80% red cell radio-iron utilization (RCU).
The blue area indicates the 288° proportion of the red cell iron turnover rate (RCIT). The tissue iron turnover rate (TIT); (PIT – RCIR) accounts for the 120° proportion as the sum of the red area (SIT) and purple area (Non-SIT).
The TIT is composed of the two kinds of tissue iron turnover rates; the TIT due to the radio-iron fixed to tissue iron components (TITf), and the TIT due to the radio-iron released from tissue iron components to plasma (TITr) within 2 weeks.
The yellow area indicates the 72° proportion of TITr.
The blue area extruding from the area-angle of RCIR into the area-angle of TIT indicates the 48° proportion of TITr at 80% red cell radio-iron utilization (RCU).
The blue area indicates the 288° proportion of the red cell iron turnover rate (RCIT). The tissue iron turnover rate (TIT); (PIT – RCIR) accounts for the 120° proportion as the sum of the red area (SIT) and purple area (Non-SIT).
The TIT is composed of the two kinds of tissue iron turnover rates; the TIT due to the radio-iron fixed to tissue iron components (TITf), and the TIT due to the radio-iron released from tissue iron components to plasma (TITr) within 2 weeks.
The yellow area indicates the 72° proportion of TITr.
The blue area extruding from the area-angle of RCIR into the area-angle of TIT indicates the 48° proportion of TITr at 80% red cell radio-iron utilization (RCU).
The blue area indicates the 288° proportion of the red cell iron turnover rate (RCIT). The tissue iron turnover rate (TIT); (PIT – RCIR) accounts for the 120° proportion as the sum of the red area (SIT) and purple area (Non-SIT).
The TIT is composed of the two kinds of tissue iron turnover rates; the TIT due to the radio-iron fixed to tissue iron components (TITf), and the TIT due to the radio-iron released from tissue iron components to plasma (TITr) within 2 weeks.
The yellow area indicates the 72° proportion of TITr.
The blue area extruding from the area-angle of RCIR into the area-angle of TIT indicates the 48° proportion of TITr at 80% red cell radio-iron utilization (RCU).
The blue area indicates the 288° proportion of the red cell iron turnover rate (RCIT). The tissue iron turnover rate (TIT); (PIT – RCIR) accounts for the 120° proportion as the sum of the red area (SIT) and purple area (Non-SIT).
The TIT is composed of the two kinds of tissue iron turnover rates; the TIT due to the radio-iron fixed to tissue iron components (TITf), and the TIT due to the radio-iron released from tissue iron components to plasma (TITr) within 2 weeks.
The yellow area indicates the 72° proportion of TITr.
The blue area extruding from the area-angle of RCIR into the area-angle of TIT indicates the 48° proportion of TITr at 80% red cell radio-iron utilization (RCU).
The blue area indicates the 288° proportion of the red cell iron turnover rate (RCIT). The tissue iron turnover rate (TIT); (PIT – RCIR) accounts for the 120° proportion as the sum of the red area (SIT) and purple area (Non-SIT).
The TIT is composed of the two kinds of tissue iron turnover rates; the TIT due to the radio-iron fixed to tissue iron components (TITf), and the TIT due to the radio-iron released from tissue iron components to plasma (TITr) within 2 weeks.
The yellow area indicates the 72° proportion of TITr.
The blue area extruding from the area-angle of RCIR into the area-angle of TIT indicates the 48° proportion of TITr at 80% red cell radio-iron utilization (RCU).
The blue area indicates the 288° proportion of the red cell iron turnover rate (RCIT). The tissue iron turnover rate (TIT); (PIT – RCIR) accounts for the 120° proportion as the sum of the red area (SIT) and purple area (Non-SIT).
The TIT is composed of the two kinds of tissue iron turnover rates; the TIT due to the radio-iron fixed to tissue iron components (TITf), and the TIT due to the radio-iron released from tissue iron components to plasma (TITr) within 2 weeks.
The marrow macrophage storage iron turnover rate, 2.8 mg/days, was almost half that of SIT.

3) Influence of extra radio-iron fixation to red cell mass
The MRCLS measured by dividing RCI by RCIT with surplus is expected to be shorter than the generally recognized normal value 120 days, because RCIT is larger than the net red cell iron turnover rate.

MRCLS of normal subjects calculated by using the data of Huff et al. became 118 days. It might be normalized by the lower RCU (75%). MRCLS by Cook, et al. and Ricketts, et al. was a little shorter, averaging 109 and 105 days, respectively, in normal subjects. The average MRCLS in 4 normal cases determined by Ricketts, et al. was 94 days. There, one case with 150 days was excluded.

4) Influence of radio-iron distribution reduction to non-erythron tissue iron components
The extra radio-iron fixation to red cell mass results in radio-iron distribution reduction to non-erythron tissue iron components.

Cook, et al. and Ricketts, et al. reported the non-erythron iron turnover rate (Non-EIT); (PIT – EIT) = (PIT – RCIT), 0.15 and 0.12 in mg/dl whole blood/day. The author converted their Non-EIT (mg/dl whole blood/day) to TIT (mg/day) according to the intercomponent proportion. The converted values became 6.0 and 5.0 mg/day each, which were evidently lower than the standard value of TIT 10 mg/day. Then, the converted values were corrected by the correction rate 0.6 for radio-iron distribution reduction. After the correction, these values became 9.2 and 10.0 mg/day.

They also reported the parenchymal tissue iron turnover rates, which seemed to correspond to SIT, 0.09 and 0.05 in mg/dl whole blood/day each in normal subjects. After the unit conversion, these values became 3.6 and 2.4 mg/day, which were evidently lower than the standard SIT 5.8 mg/day. Then, the converted values were corrected for the influence of radio-iron distribution

| Iron turnover rate (mg/day) | Not corrected → Corrected |
|-----------------------------|---------------------------|
| Tissue iron turnover rate (TIT)* | 10.0 |
| Non-erythron iron turnover rate (PIT – RCIT) | 7.0 → 9.2 |
| Non-erythron iron turnover rate (PIT – RCIT) | 3.0 → 11.0 |
| Non-erythron iron turnover rate (PIT – RCIT) converted to TIT | 6.0 → 9.9 |
| Non-erythron iron turnover rate (PIT – RCIT) converted to TIT | 5.0 → 10.0 |
| Non-erythron iron turnover rate (PIT – RCIT) converted to TIT | 6.6 → 9.2 |
| Storage iron turnover rate (SIT)* | 5.8 |
| Storage iron turnover rate assumed to be 10% of PIT | 2.7 |
| Storage iron turnover rate | 1.0 → 4.0 |
| Parenchymal iron turnover rate converted to SIT | 3.6 → 4.9 |
| Parenchymal iron turnover rate converted to SIT | 2.4 → 4.8 |

TIT* and SIT* are the boldfaced standard values not determined by ferrokinetics. The corrected values are shown to the right of the arrows. In the cases whose RCIR were not measurable, the ratio red cell iron (RCI) per whole-body iron (WBI) of normal subjects was applied for correction. References are shown in parentheses.
Radio-iron distribution bias causes errors in determining the body iron turnover by ferrokinetics.

reduction. After the correction, these values became 4.9 and 4.8 mg/day, respectively. However, these corrected values were still lower than the standard SIT 5.8 mg/day.

SIT assumed by Huff, et al.\(^1\) was 10% of PIT (2.7 mg/day). SIT reported by Pollycove, et al.\(^3\) was 1 mg/day in normal subjects. However, the value assumed by Huff, et al.\(^1\) was not suitable for correction. The value by Pollycove, et al.\(^3\) became 4 mg/day after the correction. However, it was still lower than SIT 5.8 mg/day.

DISCUSSION

1) Radio-iron turnover in normal subjects

Most of the intravenously injected radio-iron is rapidly cleared by red cell precursors in bone marrow. Plasma radio-iron uptake by red cell precursors is a one-way fixation reaction like a chemical precipitation reaction, as hemoglobin iron does not exchange with plasma iron.\(^{19}\) Therefore, the radio-iron uptake by red cell precursors increases progressively by adding the refluxed radio-iron from tissue iron components. On the other hand, the radio-iron uptake by non-erythron tissue iron components becomes progressively difficult in the lapse of time by the

Fig. 3 The general trend of radio-iron distribution in normal subjects in 2 weeks after iv radio-iron injection. The steep curve at the left indicates plasma radio-iron clearance. The radio-iron uptake peak of red cell precursors “Erythroblasts” and that of tissue iron-storing components “Tissue” appear synchronized after around 24 hours.

“Tissue” indicates the radio-iron uptake peak by non-erythron tissue (liver and spleen mostly).
The decreasing curve from the uptake peak “Erythroblasts” indicates the emigration of radio-iron labeled red cells after maturation from bone marrow to peripheral blood.
The sigmoid increasing curve indicates the increment of radio-iron labeled red cells in peripheral blood within 2 weeks.

“Red cell fixed” indicates the ratio red cell radio-iron utilization (RCU) after 2 weeks per total radio-iron injected.
The radio-iron decrease curve from the peak of “Tissue” indicates the radio-iron release from tissue to plasma.

“Tissue fixed” indicates a part of the radio-iron stayed in tissue after 2 weeks.
The dotted short horizontal line in the right upper part indicates the ratio of pre-existing red cell iron (RCI) per whole-body iron (WBI).
The difference between the ratios % RCU and % (RCI/WBI) disappears when radio-iron is completely mixed with pre-existing body iron after one year in normal subjects (14).
exponential decrease of radio-iron concentration in plasma. Then, the radio-iron uptake peaks of bone marrow erythroblasts and non-erythron tissue iron components appear synchronized around 24 hours after radio-iron injection in normal subjects. Radio-iron labeled red cell precursors, on the other hand, begin to leave bone marrow after maturation. Part of radio-iron taken up by non-erythron tissue begins to leave tissue to plasma. The proportion of radio-iron taken up by red cell precursors in bone marrow after around 24 hours is less than the radio-iron fixed to red cells within 2 weeks (RCU), which is increased by the additional red cell fixation of radio-iron refluxed from non-erythron tissue iron components.

Thus, the body radio-iron distribution after around 24 hours seems to reflect the iron partition in proportion to the iron contents of pre-existing body iron components.

Although the ferritin radio-iron uptake peaks after 24 hours in normal rat liver and spleen were demonstrated by chemical fractionation, the attempts to detect such a storage iron turnover by body surface monitoring, whole-body scanning and positron camera imaging failed due to the high background noise from radio-iron in bone marrow. If $^{52}$Fe positron CT image is followable for several days, the storage iron turnover in liver and spleen may be confirmed in humans.

2) Influence of extra radio-iron fixation to red cell mass

The process of radio-iron fixation to red cells is the same as one-way chemical precipitation reaction. Therefore, RCU reaches 80% or more 2 weeks after radio-iron injection in normal subjects, which is higher than the around 67% ratio of RCI/WBI.

The ratio RCU per RCI/WBI will be as follows:
At 80% RCU and 67% RCI/WBI: $0.8/0.67 = 1.19$; 19% increment.
At 90% RCU and 67% RCI/WBI: $0.9/0.67 = 1.34$; 34% increment.

As RCIT (PIT × RCU/100) becomes larger than the net red cell iron turnover rate, the value RCIT is not appropriate to call the “red cell iron turnover rate.” However, it is already used generally. Accordingly, the name RCIT is used here in the meaning of so-called RCIT. For this reason, red cell iron renewal rate (RCIR) is adopted as an index of the net red cell iron turnover rate.

The underestimation of MRCLS determined by the ferrokinetic method from RCI/RCIT indicated that the method was not suitable for practical use.

Pollycove, et al. assumed the existence of a large amount of labile iron pool in erythroblasts as a source of radio-iron reflux in normal subjects. To their assumption, Finch commented that the existence of such a large labile iron pool before hemoglobin synthesis was unlikely. However, the investigators of ferrokinetics after Pollycove, et al. still employed RCIT and admitted a significant amount of iron reflux from erythroblast labile iron pool to plasma in normal subjects. However, as pointed out by Finch, the existence of such a reflux seems contradictory to the rapid and effective erythropies in normal subjects.

Iron loss at the time of nucleus extrusion from erythroblasts, and that of random destruction of red cells are to occur even in normal subjects. However, such iron loss from erythron cannot be as large as such a reflux from the labile iron pool in erythroblasts.

The amount of pre-existing iron taken up by erythroblasts from plasma and that of iron released from macrophages after the sequestration of senescent red cells in normal subjects are almost the same as a constant flow through a tube.

The difference between RCIT and RCIR is produced by the excess of RCIT affected by RCU. Therefore, the difference cannot be attributed to such a reflux from erythroblasts.
Radio-iron distribution bias causes errors in determining the body iron turnover by ferrokinetics

3) Influence of radio-iron distribution reduction to non-erythron tissue iron components

The value \((1 – \text{RCU}/100)\) indicates the ratio of radio-iron distribution to non-erythron tissue after 2 weeks. It is 20% or less, but the ratio \(1 – (\text{RCI}/\text{WBI})\) is around 33% in normal subjects. Therefore, the ratio of radio-iron distribution reduction to non-erythron tissue will be as follows:

At 80% RCU and 33% RCI/WBI: \(0.20/0.33 = 0.60\); 40% reduction.

At 90% RCU and 33% RCI/WBI: \(0.10/0.33 = 0.30\); 70% reduction.

Thus, the influence of radio-iron distribution reduction to non-erythron tissue becomes more serious than that of radio-iron distribution increment to red cell mass.

After the conversion for unit and the correction for radio-iron distribution reduction, the non-erythron iron turnover rates\(^6,7\) coincided with TIT, but their parenchymal iron turnover rates\(^6,7\) were still lower than SIT. This seems to indicate the incurable errors in the storage iron turnover rate determined by ferrokinetics. Thus, the excess of RCIT caused various errors in ferrokinetics.

4) Biased radio-iron distribution in iron deficiency and iron overload

a. Iron deficiency anemia (IDA):

Despite the limitation of erythropoiesis in iron deficiency,\(^25\) PIT is slightly increased. PIT reflects both the effective and ineffective erythropoiesis.

RCU increases to nearly 100% due to the minimal radio-iron dilution with pre-existing body iron.

RCIT, affected by RCU, indicates the overestimated value of the red cell iron turnover rate. On the other hand, RCIR indicates the net red cell iron turnover rate. Then, the difference between RCIT and RCIR becomes largest in IDA.

TIT and SIT become minimal due to the highest radio-iron fixation to red cells.

Iron refractory iron deficiency anemia (IRIDA) with gene mutation\(^26\) is not taken up here, as the response of IRIDA to iron administration is different from simple IDA.

b. Hereditary hemochromatosis (HH):

The increase of radio-iron fixation to storage tissue increases PIT\(^3,6,10\) by the increase of SIT. Therefore, the increase of PIT does not imply the increase of erythropoiesis, as erythropoiesis is within the normal limit in HH, except for the state of post-phlebotomy therapy\(^27,28,29\).

RCU is decreased near the ratio RCI per WBI due to the dilution of radio-iron by a large amount of pre-existing body iron, but not by the suppression of erythropoiesis.

RCIT is increased by the increase of SIT due to the increase of radio-iron distribution to storage. Thus, the content of RCIT disagrees with the name red cell iron turnover rate. On the other hand, RCIR is within the normal limit.

TIT is increased along with the increase of SIT.

SIT cannot be determined exactly by ferrokinetics, but it can be roughly estimated from TIT by erythro-ferrokinetics in iron overloaded HH.

CONCLUSION

The extra radio-iron distribution to red cell mass is indicated by the increase of red cell radio-iron utilization (RCU) beyond the ratio red cell iron per whole body iron in normal subjects. Then, the red cell iron turnover rate (RCIT) affected by RCU exceeds the net red cell iron turnover rate that is indicated by the red cell iron renewal rate (RCIR). The excess RCIT is caused by the additional red cell fixation of radio-iron reflux from non-erythron tissue iron components in normal subjects.
The extra radio-iron fixation to red cell mass results in the reduction of radio-iron distribution to non-erythron tissue iron components. This caused the underestimation of the non-erythron tissue (TIT) and storage iron turnover rates (SIT) by ferrokinetics.

RCU and RCIT become larger in IDA than in normal subjects. On the other hand, despite the decrease of RCU, RCIT is increased by the increase of SIT in HH. Thus, the name RCIT does not correctly indicate its contents.

The erythrokinetic index RCIR is not only useful for disclosing the problems in ferrokinetics but also for revealing the essential feature of body iron turnover.

ACKNOWLEDGEMENTS

The author expresses cordial thanks to Mr. Kenji Utsumi, former staff of the Sony Corporation, for his kind cooperation and advice.

CONFLICTS OF INTEREST

None.

REFERENCES

1) Huff RL, Hennessy TG, Austin RE, Garcia JF, Robarts BM, Lawrence JH. Plasma and red cell disorders. J Clin Invest, 1950; 29: 1041–1052.
2) Huff RL, Elmlinger PL, Garcia JF, Oda JM, Cockrell MC, Lawrence JH. Ferrokinetics in normal persons and in patients having various erythropoietic disorders. J Clin Invest, 1951; 30: 1512–1526.
3) Pollycove M, Mortimer, R. The quantitative determination of iron kinetics and hemoglobin synthesis in human subjects. J Clin Invest, 1961; 40: 753–782.
4) Finch CA, Deubelbeiss K, Cook JD, Eschbach JW, Harker LA, Funk DD, et al. Ferrokinetics in man. Medicine, 1970; 49: 17–53.
5) Hosain F, Marsaglia G, Finch CA. Blood ferrokinetics in man. J Clin Invest, 1967; 46: 1–9.
6) Cook JD, Marsaglia G, Eschbach JW, Funk DD, Finch CA. Ferrokinetics: a biologic model for plasma iron exchange in man. J Clin Invest, 1970; 49: 197–205.
7) Ricketts C, Jacobs A, Cavill I. Ferrokinetics and erythropoiesis in man: the measurement of effective erythropoiesis, ineffective erythropoiesis and red cell life span using 59Fe. Brit J Haemat, 1975; 31: 65–75.
8) Saito H, Yamada H, Hirade M. Determination of effective erythropoiesis rate by ferrokinetics in various hematologic disorders. Acta Haem Jap, 1976; 39: 138–144. (in Japanese)
9) Saito H, Sargent T, Parker HG, Lawrence JH. Whole body iron loss in normal man measured with a gamma spectrometer. J Nucl Med, 1964; 5: 571–580.
10) Bothwell TH, Charlton RW, Cook JD, Finch CA. Clinical estimation of body iron stores: In: Iron metabolism in man, edited by Bothwell TH, Charlton RW, Cook JD, Finch CA. How large is the body iron reserve. pp 88–93. Internal iron kinetics: pp 327–349, 1979, Blackwell Scientific Publications, Oxford London Edinburgh Melbourne.
11) Saito H. Metabolism of iron stores. Nagoya J Med Sci, 2014; 76: 235–254.
12) Parthar A, Eubank TD, Doseff AI. Monocytes and macrophages regulate immunity through dynamic networks of survival and cell death. J Innate Immu, 2010; 2: 204–215.
13) Spalding KL, Bhardwaj RD, Buchholz BA, Druid H, Frisén J. Retrospective birth dating of cells in humans. Cell, 2005; 122: 133–43.
14) Frisen J. Life span of human cells defined: most cells are younger than the individual. CORDIS, August 12, 2005. Available at: https://cordis.europa.eu/news/rcn/24286_en.html Accessed April 17, 2018.
15) Finch CA. Body iron exchange in man. J Clin Invest, 1959; 38: 392–396.
16) Green R, Charlton RW, Seftel H, Bothwell T, Mayer F, Adams B, et al. Body iron excretion in man. A collaborative study. Am J Med, 1968; 45: 336–353.
Radio-iron distribution bias causes errors in determining the body iron turnover by ferrokinetics

17) Miura T. Iron excretion into feces in various hematologic disorders. *Jpn J Radiol*, 1968; 28: 1288–1295.
18) Berlin NI. Determination of red blood cell life span. *JAMA*, 1964; 188: 375–378.
19) Hahn PF, Bale WF, Ross JF, Hettig RA, Whipple GH. Radio-iron in plasma does not exchange with hemoglobin iron in red cells. *Science*, 1940; 92: 131–132.
20) Saito H. Studies on storage iron. Dynamic behaviors of ferritin and hemosiderin under various experimental conditions. *Nagoya J Med Sci*, 1958; 21: 288–300.
21) Saito H, Yamada H. Studies on red cell production and destruction in various hematological disorders in view of ferrokinetics. *Acta Haem Jap*, 1973; 36: 681–709.
22) Van Dyke D, Anger HO. Patterns of marrow hypertrophy and atrophy in man. *J Nucl Med*, 1965; 6: 109–120.
23) Pollycove M. Iron kinetics. In: *Discussion; Iron Metabolism: an International Symposium sponsored by CIBA at Aix-en-Provence, 1963*. edited by Gross F. pp. 148–170, 172, 1964, Springer-Verlag, Berlin Göttingen Heidelberg.
24) Finch CA. In: *Discussion; Iron Metabolism: an International Symposium sponsored by CIBA at Aix-en-Provence, 1963*, edited by Gross F. pp 172, 1964, Springer-Verlag, Berlin Göttingen Heidelberg.
25) Finch S, Haskins D, and Finch CA. Hematopoiesis following phlebotomy. Iron as a limiting factor. *J Clin Invest*, 1950; 29: 1078–1081.
26) Finberg KE. Iron refractory iron deficiency anemia. *Sem in Hematol*, 2009; 46: 378–386.
27) Milder MS, Cook JD, Finch CA. Idiopathic hemochromatosis: an interim report. *Medicine*, 1980; 59: 34–49.
28) Crosby WH. Treatment of hemochromatosis by energetic phlebotomy. One patient’s response to the letting of 55 litres of blood in 11 months. *Brit J Haemat*, 1958; 4: 82–88.
29) Sargent T, Saito H, Winchell HS. Increased iron absorption in hemochromatosis before and after phlebotomy therapy. *J Nucl Med*, 1971; 12: 660–667.