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Clinical Evaluation of Red Cell Volume Distribution Width (RDW)

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New automated blood cell analyzers, Coulter Counter Model S-Plus® series provide an index of red cell volume distribution width (RDW) or heterogeneity and a histogram display of red cell volume distribution. We evaluated the clinical significance of RDW by determining the normal range of RDW in healthy adults, children, and newborns and the change of RDW in pediatric patients with various hematologic diseases. The normal ranges of RDW in adults, children, and newborns were 12.3±0.8, 13.0±1.0, and 17.1±1.7% respectively. Increases in RDW were observed in patients with iron deficiency and in those receiving iron therapy, as in those with early iron deficiency. Patients with chronic disease, acute hemorrhage, and aplastic anemia with no transfusion in the previous four months had normal RDW. In contrast, patients with immune hemolytic anemia, hereditary spherocytosis, mechanical hemolytic anemia, acute leukemia, chronic myelocytic leukemia, and chronic hepatobiliary disease had high RDW, as did those with solid tumor and malignant lymphoma during chemotherapy. Among patients with acute leukemia during chemotherapy, RDW was more increased if accompained by macrocytosis than by normocytosis. It was found that the RDW was proportional to the % reticulocyte. We tried to classify anemia, based on RDW and mean corpuscular volume (MCV) and to guide the diagnosis from the peripheral blood analysis in pediatric patients. The distinction of iron deficiency anemia from the anemia of chronic disease and the detection of early iron deficiency was improved. A change in RDW according to storage time at room temperature was not observed. From this study, RDW could be used as a sensitive parameter of red cell anisocytosis. Thus we recommend the use of these new variables in the initial classification of anemia in pediatric patients.

Key Words: Red cell volume distribution width (RDW), MCV, classification of anemia, automated blood cell counters

Although the diameter of the red blood cell was measured accurately by Jurlin in 1718, the first quantitative assessments of variation in red blood cell diameter measurements were reported by Price-Jones (1910, 1922, 1933) using ocular micrometry on fixed stained peripheral blood smears from normal individuals and from patients with a variety of anemias. He postulated that difference in size and range variation might be diagnostically useful. However, microscopic measurement of red blood cell size was tedious and time consuming, had limitations because of significant subjectivity associated with visual inspection.

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The change from chamber counts to flow cytometry for routine blood counts in some recently designed automated cell counters had brought not only improved speed and precision, but also new measurements permitted by the analysis of large numbers of single-cell measurements. Measured as a coefficient of variation (CV) and reported as RDW, the heterogeneity of distribution of red cell size (the equivalent of anisocytosis in analysis of the peripheral blood smear) now forms part of the reported automated blood count.

The present study was, therefore, designed to evaluate the clinical significance of RDW by determining the normal ranges of RDW in healthy adults, children, and newborns and by observing the change of RDW in children with various hematologic diseases. We also evaluated how RDW complements the MCV to improve the classification of anemia from the blood count alone.

MATERIALS AND METHODS

Complete blood counts were obtained with Coulter Counter Model S-Plus II, III® (Coulter Electronics, Hialeah, FL) with standard calibration according to the manufacturer's instructions.

A 12-parameter analysis of blood was obtained automatically. Included were the red blood cell count (RBC), hemoglobin (Hgb), hematocrit (Hct), MCV, mean cell hemoglobin concentration (MCHC), RDW, and a histogram showing the distribution of size among approximately 10^5 red cells of the sample. Daily quality control checks were performed using a stable commercially prepared reference blood (4C Plus®, Coulter Electronics). Three to four milliliters of blood were collected by venipuncture into an evacuated tube containing K_3 EDTA (tripotassium ethylenediamine tetraacetic acid) and blood counts were performed within 2 hours of sample collection.

The specimens for measurements of normal ranges of RDW in adults were collected from Severance Hospital personnel at the Yonsei University College of Medicine undergoing periodic evaluation. Among those subjects, 86 males and 89 females were used as controls. RDW values were tabulated as normal only when other hematologic parameters and laboratory findings were normal. In pediatric age groups, 54 newborns who were delivered at the same hospital and 210 children who visited the Well Baby Clinics on vaccination schedules were used as controls. All of those were apparently clinically and hematologically normal. The specimens for observing the change of RDW in various hematologic diseases were collected from 505 patients who were admitted to Department of Pediatrics in the same hospital between Jan. 1984 and Feb. 1985.

Serum iron and total iron binding capacity (TIBC) were determined on the DuPont Automatic Clinical Analyzer (aca®, Dupont, Wilmington, DE). A patient was considered to be early iron deficient when Hgb was normal or decreased, MCV was normal, and the percent of iron saturation was less than 20.

The normal values of Hgb and MCV according to each age group followed the criteria of Saarinen and Siimes (1978) and Dallman and Siimes (1979). The classification of MCV category (high, normal, or low) and RDW category (normal or high) is based on the mean values of MCV and RDW obtained from statistical probabilities calculated as applicable using a two-side t-test. Reticulocyte counts were obtained by counting reticulocytes on a smear made from 0.5mL whole blood incubated for 20 minutes with an equal volume of 1% methylene blue.

RESULTS

Estimated normal ranges of RDW

The normal range of RDW in adults was 12.3±0.8% and no significant difference was noted by sex. The normal ranges of RDW in newborns, 1, 3, 6, 8, 15, 18, and 48 month old children were 17.1±1.7, 14.7±1.0, 12.3±0.8, 13.1±0.9, 13.0±1.0, 12.9±0.7, 13.1±0.8, and 12.5±0.6% respectively (Table 1, Fig. 1). The normal RDW values in newborns and 1 month old neonates were higher than those of other children's groups but there was little difference in RDW from 3 month old children to adults ($p>0.05$).

RDW values in iron deficiency with various clinical conditions

Increases in RDW were observed in iron deficient patients who were diagnosed serologically or by bone marrow examination and in those receiving therapy for iron deficiency, as in those with early iron deficiency, even if both MCV and Hgb were in the normal range. Iron deficient patients with Tetralogy of Fallot showed no anemia but RDW was increased (Table 2).

The RBC histogram reflects the native size of red blood cells or of any other particles in the red cell size range. The red cell histogram of one patient with iron deficiency showed an increased skew to the left due to marked microcytosis. But, with iron therapy, the red cell histogram widened; consequently, the RDW increased (Fig. 2).

The correlation between RDW and % reticulocyte

In 20 cases of iron deficiency, the values of RDW

Table 1. Estimated normal mean values of RDW

Age	N	RDW (mean ± S.D.)
Newborn	54	17.1 ± 1.7
Infancy and childhood	210	13.0 ± 1.0
1 month	30	14.7 ± 1.0
3 month	30	12.3 ± 0.8
6 month	30	13.1 ± 0.9
8 month	30	13.0 ± 1.0
15 month	30	12.9 ± 0.7
18 month	30	13.1 ± 0.8
4 years	30	12.5 ± 0.6
Adult	175	12.3 ± 0.8
male	86	12.1 ± 0.5
female	89	12.5 ± 1.0

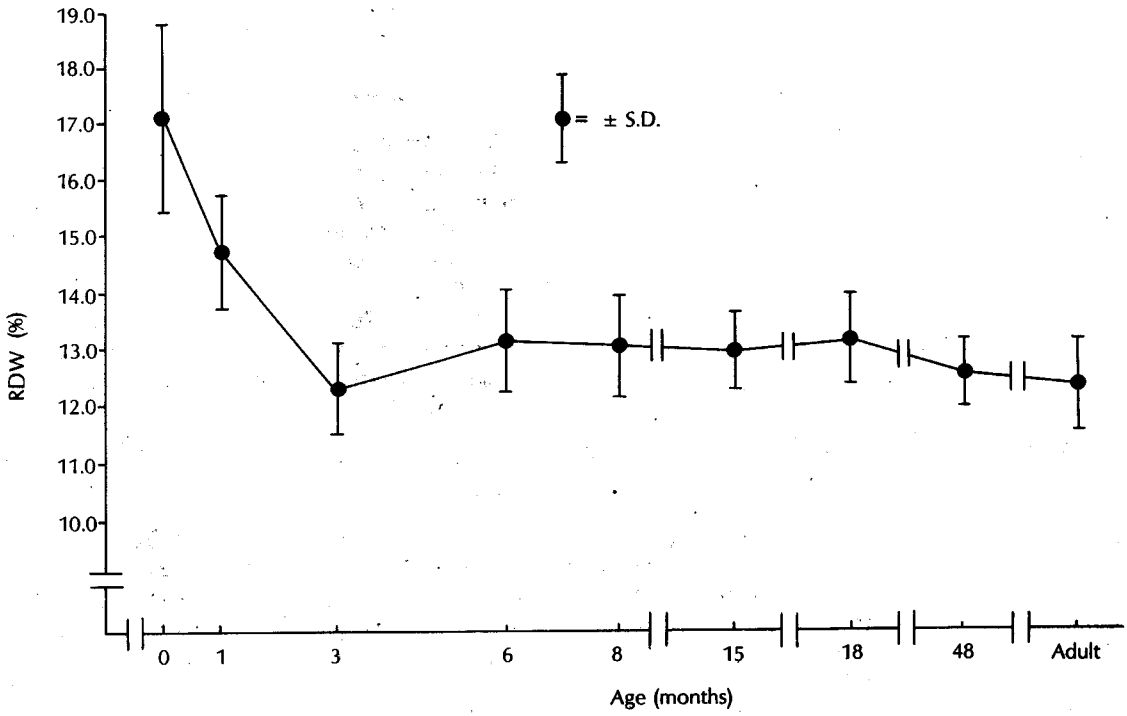

Fig. 1. The normal RDW values in different age groups. Each black circle represents mean RDW values.

Table 2. RDW values and other hematologic findings in iron deficiency with various clinical conditions

	N	RBC# ($\times 10^{12}$/L)	Hgb (gm/dl)	MCV (fl)	Iron (μg/dl)	TIBC (μg/dl)	Satn* (%)	RDW (%)	Reticulocytes (%)
Iron deficiency	55	4.56±0.64	9.4±1.7	64.2±7.6	39.2±21.6	379.6±64.0	9.5±5.7	18.1±2.8	1.3±0.6
Absent bone marrow iron	16	3.88±0.46	7.1±1.7	58.2±8.8	–	–	–	21.5±4.5	1.2±0.6
Early iron deficiency	27	4.32±0.44	11.2±1.0	77.7±4.6	44.0±20.2	310.8±85.2	13.9±6.2	16.1±2.0	1.1±0.7
Iron deficiency with TOF	12	6.71±1.05	14.4±3.3	66.0±8.3	48.7±11.4	443.8±63.5	11.2±3.2	21.2±3.6	1.7±0.1
Therapy of iron deficiency									
before treatment	20	4.76±1.33	9.7±2.8	64.3±8.8	–	–	–	19.5±3.7	1.5±0.6
during treatment	20	5.06±1.34	11.5±3.0	73.1±8.9	–	–	–	25.3±4.4	2.5±0.9

#; mean ± S.D.
*; Iron saturation

and % reticulocyte were checked before and during iron therapy, and then an attempt was made to correlate the RDW with % reticulocyte. There was a direct relationship between RDW and % reticulocyte (Fig. 3).

RDW findings of various hematologic diseases

Patients with chronic disease, acute hemorrhage, and aplastic anemia with no transfusion in the previous four months had normal RDW. On the contrary, patients with immune hemolytic anemia, hereditary spherocytosis, mechanical hemolytic anemia, chronic myelocytic leukemia, chronic hepatobiliary disease, and acute leukemia had high RDW, as did those with solid tumor and malignant lymphoma during chemotherapy. Among the patients with acute lymphocytic and nonlymphocytic leukemia during chemotherapy, RDW was more increased if accompanied by macro-

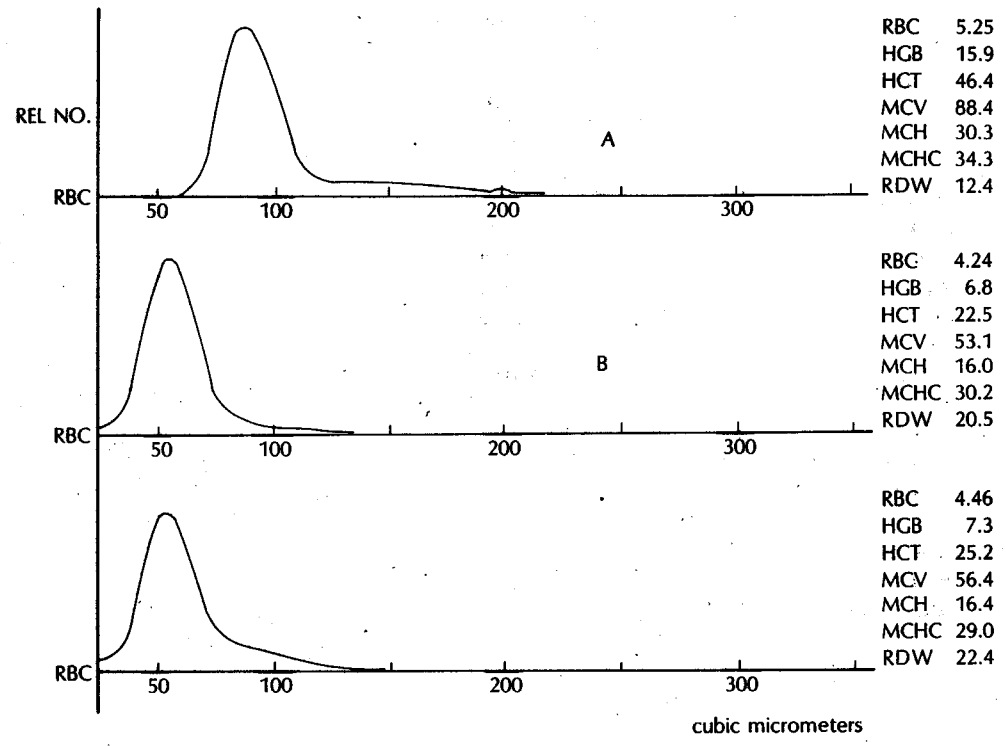

Fig. 2. The red cell histograms of iron deficiency anemia. A. Reference normal histogram. B. 14 year old male patient with iron deficiency anemia, serum iron 0 µg/dl, TIBC 650 µg/dl, reticulocyte 0.5%. C. Patient's histogram after iron therapy for 5 days, reticulocyte 3.5%.

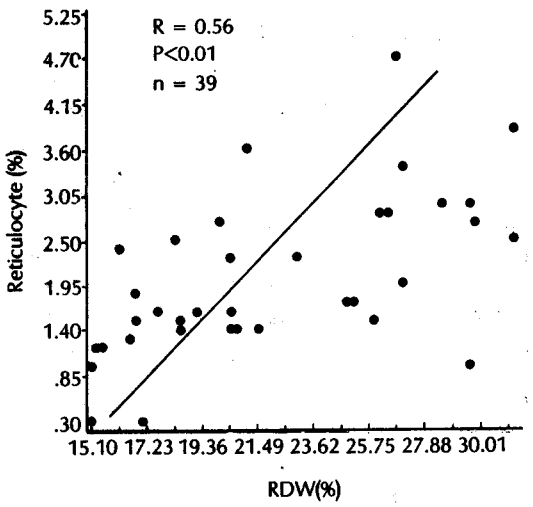

Fig. 3. The correlation between RDW and reticulocyte in cases of iron deficiency. Equation for linear regression line is y = −0.3003 + (0.1084)x.

cytosis than by normocytosis. There was little difference in RDW between cyanotic congenital heart disease (CHD) and noncyanotic CHD despite polycythemia in cyanotic CHD. In transfused patients with various diseases, there was also no significant difference in RDW between pre and post transfusion (Table 3).

The red cel histogram of a patient with acute lymphocytic leukemia during chemotherapy showed an increased skew to the right, RDW, and macrocytosis. The example of red cell histograms in one case of aplastic anemia with multiple transfusions within the previous 4 months and in a multiply transfused patient after acute hemorrhage can also be seen in Fig. 4.

Classification of anemia based on MCV and RDW

From the above data we have constructed a classification of anemia based on the two directly measured indices of red cell size: MCV and RDW. Patients with a given anemic disorder were assigned to the MCV category (high, normal, or low) given in a traditional classification and to the RDW category (normal or high), as shown in Fig. 5.

Table 3. RDW findings in various hematologie diseases

Diagnosis	N	RBC* ($x10^{12}$/L)	Hgb (gm/dl)	MCV (fl)	RDW (%)
Normal subjects	210	4.40±0.52	12.2±0.9	82.3±6.1	13.0±1.0
Chronic disease©	50	3.91±0.64	10.8±1.3	81.7±6.1	13.6±1.4
Congenital heart disease					
cyanotic group	34	6.04±0.80	17.3±2.2	86.7±3.7	13.6±1.5
noncyanotic group	29	4.38±0.31	11.9±0.7	83.1±4.1	13.4±1.0
After hemorrhage	37	3.56±0.71	9.9±1.8	83.6±5.4	13.2±1.0
Aplastic anemia	17	2.32±0.72	7.5±2.1	93.5±6.2	13.7±1.3
Transfusion					
before transfusion	30	2.60±0.99	7.6±2.6	87.5±7.7	15.6±3.1
after transfusion	30	3.70±0.84	10.9±2.2	88.9±5.2	15.5±3.1
Immune hemolytic anemia	7	2.02±0.54	6.7±1.8	99.1±5.3	16.5±2.2
Hereditary spherocytosis	4	2.48±0.72	7.6±1.5	95.1±9.2	23.6±3.6
Chronic hepatobiliary disease	10	3.89±0.51	10.5±1.1	82.5±5.6	16.3±2.0
Prosthetic heart valve					
Without fragmentation	5	4.41±0.25	12.2±0.8	85.5±4.3	13.5±1.2
With fragmentation	1	2.63	8.2	78.2	19.8
Acute nonlymphocytic leukemia					
pretreatment	12	2.26±0.43	7.2±1.4	93.5±4.9	16.1±2.5
chemotherapy; normocytosis	4	2.93±0.92	8.8±2.6	87.7±0.3	14.1±0.8
chemotherapy; macrocytosis	22	3.12±0.65	9.6±1.8	92.9±6.1	15.5±1.1
Acute lymphocytic leukemia					
pretreatment	25	2.65±0.87	7.7±2.3	84.4±9.2	17.1±3.8
chemotherapy; normocytosis	13	3.84±0.79	10.6±2.0	81.6±3.5	15.5±3.6
chemotherapy; macrocytosis	48	3.34±0.72	10.5±2.0	93.5±5.1	18.2±3.1
Chronic myelocytic leukemia	4	4.08±1.17	11.6±3.5	87.3±6.3	15.6±1.6
Solid tumor					
before chemotherapy	6	4.29±0.26	11.7±0.7	82.6±2.7	13.4±1.1
after chemotherapy	24	4.20±0.58	11.4±1.8	79.6±3.5	16.0±2.0
Malignant lymphoma					
after chemotherapy	13	3.99±0.88	11.2±2.5	84.3±4.9	16.3±1.5

©; Rheumatoid arthritis, tuberculosis, seizure disorder, osteomyelitis, empyema and renal insufficiency were included.
*; mean ± S.D.

The change in RDW values according to storage time

The change in RDW values which were measured at different intervals after collection was studied with anticoagulated (EDTA) blood obtained from 10 normal subjects who were students in Yonsei University College of Medicine. A change in RDW values according to storage time was not observed (Table 4).

DISCUSSION

The concept of cell volume measurement in suspension was introduced as a commercial proposition by Coulter (1956) using the aperture impedance method and since then, tentative work on the sizing of cells in the peripheral blood has been performed on single aperture general purpose instrument linked to a pulse height analyzer e.g. Coulter Model ZBI/Coulter Channelyzer C1000 System. The emergence of such systems made possible the measurement of the volume of cells in suspension with improved precison and accuracy and in addition eradicated the tedium and subjectivity of earlier methods. But the MCV represents the average of all cells measured and does not reveal heterogeneity within the cell population under study. More recently developed counters exemplified by the Model S-Plus series routinely provide red cell volume distribution curves. Between 1962 and 1968 a number of investigators (Brecher *et al.* 1962; Barr and Zeitler 1964;

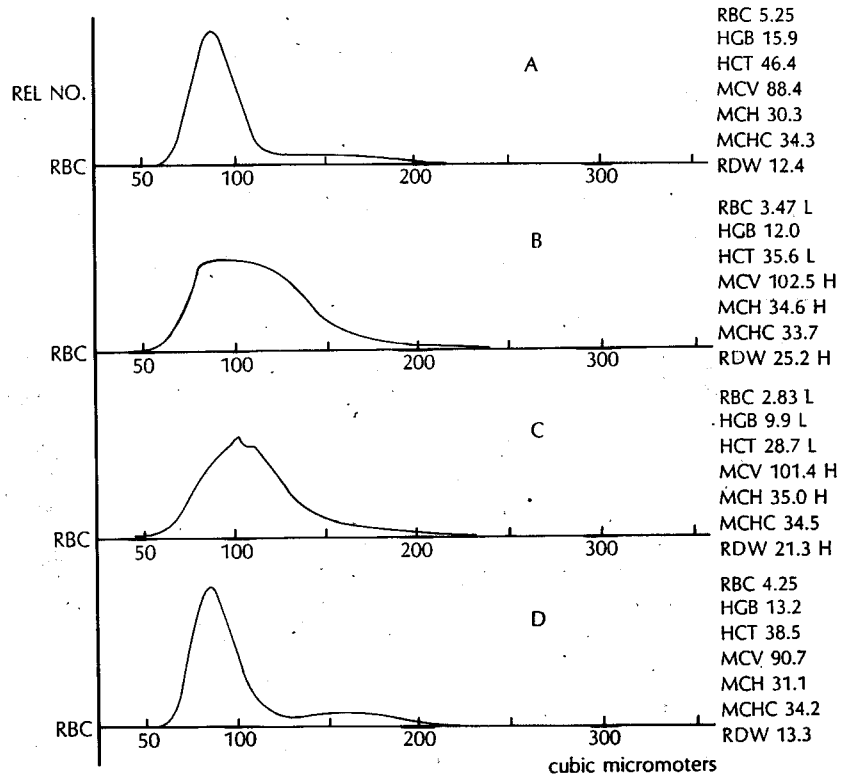

Fig. 4. *The red cell histograms of acute lymphocytic leukemia, aplastic anemia, and after transfusion. A. Reference normal histogram. B. 5 year old male patient with acute lymphocytic leukemia. a remission induction period with myelotoxic chemotherapy. C. 9 year old male patient with aplastic anemia, multiply transfused. D. 1 year old female patient with upper G-I bleeding, multiply transfused: before transfusion, Hgb 5.8gm/dl, MCV 82.8fl, RDW 13.4%.*

Lushbaugh and Lushbaugh 1965; Van Dilla and Spalding 1967; Bull 1968) analysed various facets of red cell volume distribution by aperture impedance.

There are only two candidate theoretical curves to be considered in the case of red blood cell volume distribution, namely the normal distribution (Gaussian) curve favoured by some authors (Bessman and Johnson 1975; Bessman 1980b) and the log normal distribution curve favoured by others (England and Down 1974; England *et al.* 1976). Both groups have subsequently published analyses on the use of red cell volume distribution in a variety of disease states and in particular on their value in the recognition of early iron deficiency and in the differentiation of iron deficiency anemia from heterozygous beta thalassemia (England and Down 1974; England *et al.* 1976; Bessman and Banks 1980). Increases in CV have been observed in hemoglobinopathies (Bessman 1980b; Hammersley *et al.* 1981), transfusion (Bessman 1980b), iron deficiency (Bessman and Johnson 1975; Bessman and Feinstein 1979; Bessman 1980a, 1980b), megaloblastic anemia (Bessman and Johnson 1975; Bessman 1977b, 1980b), sideroblastic anemia (Bessman 1980b), cold agglutinins (Bessman and Banks 1980), and in therapy for nutritional deficiencies (Bessman 1977a, 1977b).

The original Coulter Counter Model S-Plus® analyzed red cell volume distribution by calculating a parameter proportional to the CV called RDW. RDW is measured by progressively lowering the threshold circuit until 80%, and then only 20%, of the red cells will pass through. RDW = (80th % volume−20th % volume/80th % volume+20th % volume) ×100×0.66. The factor 0.66 is used to index the average normal RDW to a value of 10.0. The normal RDW range by this method is 8.5 to 11.3 with a mean of 9.9 (Rowan *et al.* 1979). However, RDW is only proportional to CV if the red cell volume has a Gaussian distribution. If the red cell size distribution is skewed due to changes from varying causes, RDW may not accurately quantitate anisocytosis (Cornbleet and Buechel 1983). Other studies indicate that RDW may not be

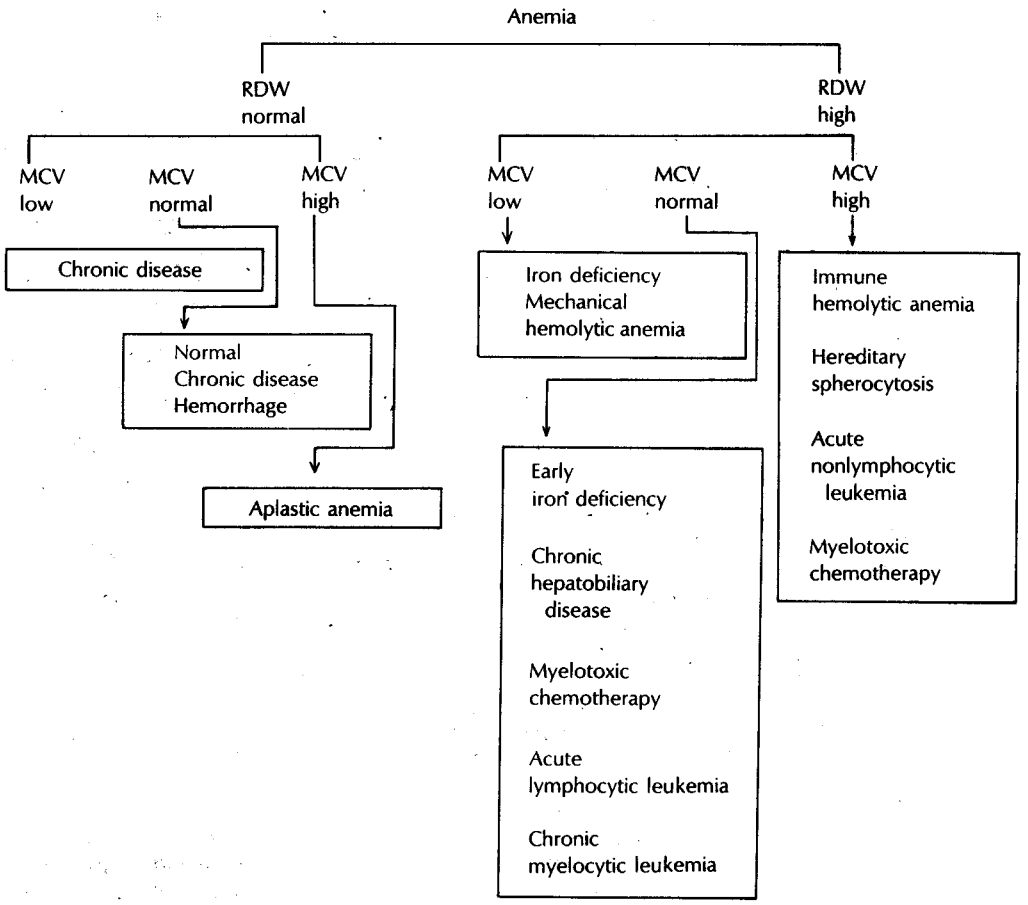

Fig. 5. *Classification of anemias based on MCV and RDW.*

Table 4. The change in RDW values according to storage time

	0hr	1hr	2hr	4hr	6hr	24hr
Mean	12.68	12.71	12.80	12.84	12.86	12.84
±S.D.	0.55	0.57	0.63	0.69	0.62	0.51
P	–	>0.2	>0.2	>0.2	>0.2	>0.2

* N=10

as sensitive as CV in detecting the anisocytosis of iron deficiency (Bessman 1980a; Cornbleet and Buechel 1983). In addition, conflicting reports exist regarding normal range for RDW (Rowan *et al.* 1977; Hammersley *et al.* 1981; Bessman 1981), storage stability (Bessman 1980a; Haiflich and Cornblett 1980; Cornbleet and Buechel 1983) and the ability to distinguish between iron deficiency and heterozygous beta thalassemia (Izzo and Ferrari 1982).

In the S-Plus II a total of 75,000 cells may be accumulated to generate a representative volume distribution histogram. The mean cell volume is obtained from this distribution by Simpson's integration, a new method for MCV determination. The RDW calculation is that from any volume distribution histogram the information below 20% of scale is removed and the CV of the remainder of the distribution calculated using the 16th and 84th% volumes. The CV of the truncated distribution is then scaled up by a factor of 1.15 to compensate, and this modified CV is called the RDW. The normal range for this S-Plus measurement is 12.7±1.0 (Rowan 1983). But the nor-

mal value depends on the technology of the instrument. However, it does emphasize that RDW should represent a true CV of the red blood cell volume distribution and that normal values should be established for each instrument (Bessman 1984).

In this study the normal values of adults and children are 12.3±0.8 and 13.0±1.0 which are similar to the study of Bessman *et al.* (13.4±1.2) in 1983. In newborns and neonates the normal values are higher than those of other children groups, but the study of normal values in more subdivided age groups is required for the diagnosis of neonatal hematologic diseases such as other red blood cell parameters.

Nutritional deficiency, whether of iron, folate, or vitamin B12, always causes an increased red cell volume heterogeneity. While these patients are anemic on the average, even those who are not anemic have a high RDW. As the nutritional deficiency progresses, successivly more abnormal cells are produced and admixed in the peripheral blood (Bessman 1980b). In early or mixed nutritional deficiency, RDW is high, while MCV remains within the normal range (Bessman *et al.* 1983). In this study, increased RDW values also can be seen in both iron deficiency anemia and early iron deficiency. In addition, alterations in the size of red blood cells brought about by specific treatment of deficiency diseases would be expected to increase red blood cell size variability. This has been clearly shown by Bessman in 1977a, b. In those studies it was apparent that the reticulocyte response associated with treatment contributed significantly to the RDW increases. Roberts and Badawi in 1985 reported that the RDW was proportional to the reticulocyte count and might lie in its capacity to reflect active erythropoiesis.

In contrast, normal RDW accompanies pure hypoproliferative anemia resulting from chronic disease, marrow toxicity, or aplasia, independent of the MCV. Thus, early iron deficiency has a high RDW and a normal MCV in contrast to chronic disease, which has a normal RDW and MCV; more advanced iron deficiency has a high RDW and a low MCV, in contrast to thalassemia minor, which has a normal RDW and a low MCV (Bessman *et al.* 1983). The distinction by RDW between iron deficiency and heterozygous thalassemia (Bessman and Feinstein 1979) or chronic disease (Bessman 1980b) recently has been confirmed for patients with low MCV (Kaye and Alter 1982). Similar to Lewis' experience (Lewis and Verwilghen 1974), our patients with aplastic anemia had a high MCV unless they had been transfused. Since the RDW is normal, such aplastic states are associated with a normal RDW and a high MCV in contrast to patients with folate or vitamin B12 deficiency (high RDW and MCV).

In hemolytic disorders, "shift" reticulocytosis and therefore an increased MCV is proportional to the duration and degree of anemia (Weiser and Kociba 1982). When reticulocytosis is due to transient blood loss or hemolysis or to compensated hemolytic anemia, reticulocytes are only 5-8% larger than and nearly as heterogeneous as the cells into which they mature (Clarkson and Moore 1976; Gilmer and Koepke 1976), and the MCV and RDW are normal. Therefore, in increased red cell destruction from any cause and with any MCV, nonanemic compensated disorders are homogeneous; anemic disorders are heterogeneous (Bessman *et al.* 1983). In this study, a high MCV and RDW could be seen in anemic disorders such as immune hemolytic anemia and hereditary spherocytosis.

Cold agglutinin diseases and erythrocyte fragmentation all have artifactually abnormal MCV and RDW because flow technology defines red cells by volume thresholds instead of hemoglobin pigmentation. Any cell 36-360 fL will be counted as a red cell; any spurious cell that is >1% as numerous as the red cells will influence the reported values. The characteristic volume distribution histograms may be the initial suggesstion of red cell fragmentation or cold agglutinin (Bessman *et al.* 1983; Rowan 1983). In this study we experienced one case of erythrocyte fragmentation accompanied by artificial cardiac valvular replacement. That case showed a low MCV and a high RDW.

Among patients with acute lymphocytic and nonlymphocytic leukemia, RDW was increased before chemotherapy differently from the study of Bessman *et al.* in 1983. In our cases, some patients received treatment at local clinics, such as transfusion, before admission to our hospital, but the RDW was definitely increased before chemotherapy and MCV was normal in acute lymphocytic leukemia and high in acute nonlymphocytic leukemia which were similar to the study of Kim *et al.* in 1985. In patients with chronic myelogeneous leukemia, the RDW was increased slightly and MCV was normal. The anemia accompanied by chronic hepatobiliary diseases was relatively well classified by increased RDW and normal MCV in contrast to the study of Bessman *et al.* in 1983.

A decrease in RDW with prolonged storage of the specimen at room temperature was observed and might contribute to erroneous patients results according to Coulter S-Plus® (Haiflich and Cornbleet 1980; Cornbleet and Buechel 1983). But in our study the measurement of new RDW by Coulter Counter S-Plus III® was more accurate, so that a change in RDW according to storage time was not observed.

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