

Blood Volume in Monoclonal Gammopathy

By Raymond Alexanian

The plasma volume, red cell volume, or both were measured in 170 normal, anemic, or polycythemic subjects. For anemic subjects without a serum protein abnormality or splenomegaly, the relationship between hematocrit and red cell volume was linear and predictable. In patients with a serum monoclonal globulin on electrophoresis, the plasma volume was significantly increased for the hematocrit in 30%, and the total blood volume was increased in 45%. The frequency of an ele-

vated plasma volume was higher in patients with a markedly increased level of monoclonal protein. Reductions of abnormal proteins with chemotherapy were associated with declines in plasma volume. For a specific concentration, the serum viscosity was highest in patients with IgM proteins and lowest in patients with IgG globulins. Marked elevations in viscosity were noted only in sera with macroglobulinemia or with more than 5 g/dl of IgG or IgA globulins.

NUMEROUS MEASUREMENTS of blood volume have been conducted in patients with hematologic disorders. The relationship between hematocrit and red cell volume has been considered unpredictable, and the necessity of red cell volume assessments for the precise definition of anemia and erythrocytosis has been emphasized.¹⁻⁴ An increased plasma volume has been documented in many patients with splenomegaly, multiple myeloma, or macroglobulinemia.⁵⁻⁷ Yet the relationship of plasma volume and viscosity to the type and level of the monoclonal globulin has not been fully clarified. This report summarizes results of plasma volume, red cell volume, and serum viscosity determinations in patients with multiple myeloma and macroglobulinemia. In the absence of serum monoclonal globulins, there is a predictable relationship between the hematocrit and the red cell volume. For patients with abnormal proteins, the plasma volume is greater than expected for the hematocrit in a large fraction of the patients. The serum viscosity is increased primarily in patients with macroglobulinemia or very high concentrations of IgG or IgA globulins.

MATERIALS AND METHODS

The red cell volume, plasma volume, or both were measured in 170 human beings summarized in Table 1. The control population consisted of 16 healthy volunteers in whom the range, mean, and 1 SD for red cell volume was 950-1300 ml/sqm (mean 1100 $\pm$ 130). The upper limit of the normal range was 1900 ml/sqm for plasma volume and 2800 ml/sqm for total blood volume.

Blood volume studies were conducted in 140 consecutive patients with chronic anemia. Forty-two with bone marrow failure had a decreased red cell volume due to aplastic anemia, sideroblastic anemia, lymphoma, myeloma, or solid tumors, but without splenomegaly or a serum protein abnormality; 98 had serum monoclonal globulins due to myeloma or macroglobulinemia.

From the Department of Medicine, The University of Texas M.D. Anderson Hospital and Tumor Institute, Houston, Texas.

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Address for reprint requests: Raymond Alexanian, M.D., Department of Medicine, The University of Texas M.D. Anderson Hospital and Tumor Institute, Houston, Texas 77025.

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Table 1. Patient Population

	No. Patients	Median Age	Hematocrit Median and Range	Mean ± 1 SD
Normal red cell volume				
Normal volunteers	16	32	47 (42-50)	47 ± 2
Increased red cell volume				
Secondary erythrocytosis	14	51	61 (56-72)	61 ± 5
Decreased red cell volume				
Myeloma with only				
Bence Jones protein	12	53	34 (21-42)	34 ± 6
Other bone marrow diseases				
without splenomegaly	30	57	32 (19-45)	32 ± 7
Serum monoclonal gammopathy				
Multiple myeloma				
Serum IgG peak	68	64	29 (14-46)	30 ± 6
Serum IgA peak	20	56	30 (20-46)	32 ± 8
Macroglobulinemia	10	65	26 (19-43)	29 ± 6

Studies in the latter patients with abnormal serum globulins, when compared with those in anemic patients without a protein abnormality, defined the effect of serum monoclonal proteins on the plasma volume and red cell volume. Fourteen patients with secondary erythrocytosis due to pulmonary disease were also evaluated to document the changes associated with a high red cell volume. Only patients previously untreated by chemotherapy, splenectomy, or phlebotomy were included. No patient was included with other causes for an increased plasma volume such as heart failure, pleural effusion, liver disease, or renal disease with a blood urea nitrogen greater than 35 mg/dl. Except for five patients with macroglobulinemia and mild splenomegaly, no patient with an enlarged spleen was included. The age distribution and hematocrit values are presented in Table 1.

The red cell mass was measured in 119 human beings with ^{51}Cr -labeled red cells by a gravimetric technique as previously described;³ microhematocrit determinations on venous blood samples were performed in triplicate. The plasma volume was measured simultaneously with ^{125}I -labeled albumin (Albumotope, W. R. Squibb & Sons); the linear extrapolation of at least three measurements over a 15-min interval defined the amount of plasma radioactivity immediately after the isotope injection.⁸ The total blood volume was derived from the sum of the measured red cell and plasma volumes. The serum viscosity was measured at 37°C with an Ostwald capillary viscometer, and the time in seconds was expressed relative to distilled water at the same temperature. Each patient included in this report had at least one of these studies, and all procedures were conducted in 49 of the 98 patients with a serum protein abnormality.

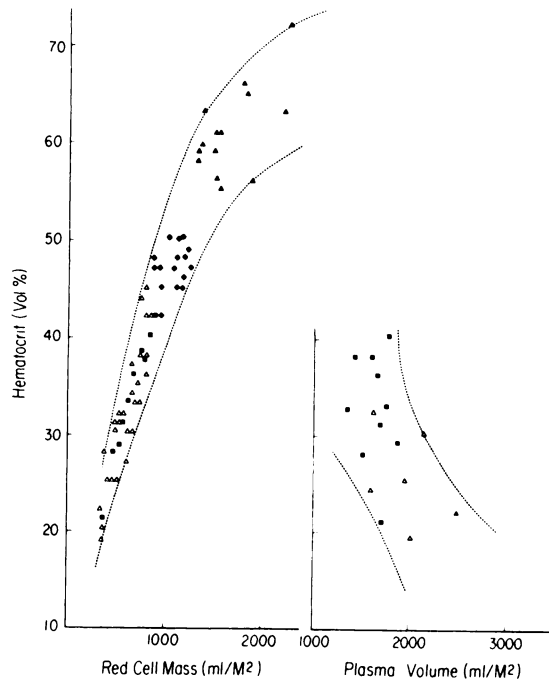
RESULTS

Control studies. The control ranges for the relationship between the venous hematocrit and the red cell volume, as well as between the hematocrit and the plasma volume, were defined from studies in normal subjects, patients anemic from bone marrow failure without splenomegaly, and patients with secondary erythrocytosis (Fig. 1). When the hematocrit was less than 40, there was a linear relationship between the hematocrit and red cell volume in accordance with the following regression line calculated by the least squares method:

$$\text{Red cell volume (ml/sqm)} = \frac{\text{hematocrit (vol/dl)} - 9}{0.037}$$

In anemic patients without an abnormal serum protein or splenomegaly, this curve predicted the red cell mass from the hematocrit to within 20% of the mea-

Fig. 1. Relationship between hematocrit and red cell volume, and between hematocrit and plasma volume. Results in normal subjects ($\diamond$), patients anemic from marrow failure without myeloma or splenomegaly ($\triangle$), anemic patients with only Bence Jones proteins ($\blacksquare$) and patients with secondary erythrocytosis ($\blacktriangle$) are compared. Dotted lines define the range for all red cell mass results and the 90% confidence interval for individual plasma volumes.



sured value. For hematocrit values greater than 50, there was a progressively greater elevation in red cell volume with serial increments in hematocrit (Fig. 1). Similarly, a linear regression line was calculated for the increasing plasma volume associated with increasing degrees of anemia below a hematocrit of 40.

$$\text{Plasma volume (ml/sqm)} = \frac{\text{hematocrit (vol/dl)} - 60}{-0.018}$$

The dotted lines in Fig. 1 defined the 90% confidence limits for individual values of plasma volume for a specific hematocrit.⁹ The total blood volume did not exceed 2800 ml/sqm in any normal or anemic subject.

Multiple myeloma and macroglobulinemia. Myeloma patients producing only Bence Jones protein had a red cell volume and plasma volume appropriate for the hematocrit (Fig. 1). As indicated in Fig. 2A, 26% of myeloma patients with a serum monoclonal globulin had an increased plasma volume with no difference in the frequency of patients with IgG or IgA myeloma proteins (25% and 29%, respectively); the frequency of an elevated plasma volume was higher in patients with an abnormal globulin level above 4 g/dl (29%) than in those with a concentration equal to or less than this level (13%), but this difference was not significant ($p > 0.2$). Of 14 patients with a hematocrit of 40 or more, only one had an elevated plasma volume. The total blood volume exceeded 2800 ml/sqm in 45% of patients with IgG or IgA globulin peaks. Six of nine patients (67%) with monoclonal macroglobulinemia also showed an increased plasma volume (Fig. 2A), along with a total blood volume greater than 2800

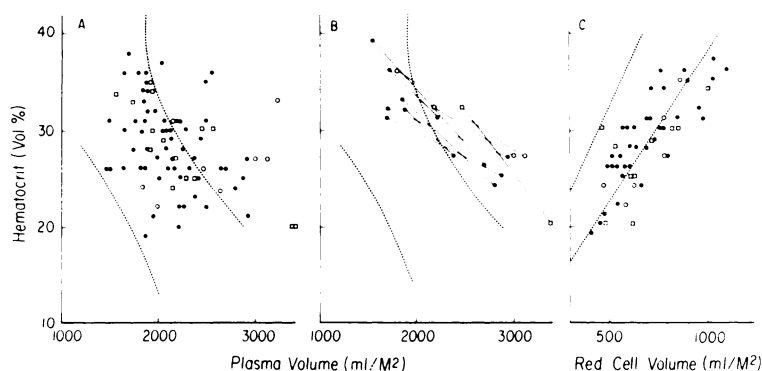


Fig. 2. (A,B) Relationship between hematocrit and plasma volume in anemic patients with serum monoclonal gammopathy, in comparison with the control range for plasma volume defined in Fig. 1. Results in patients with increased IgG globulins ($\bullet$), IgA proteins ($\square$), and IgM globulins ($\circ$) are compared. Changes in the increased plasma volume after chemotherapy are indicated for nine patients in whom the pretreatment serum monoclonal globulin ranged from 5.7 to 8.0 g/dl and posttreatment values ranged from 0.6 to 3.1 g/dl. (C) Increased red cell volume for the hematocrit in most patients with an abnormal serum globulin in comparison with the control range defined in Fig. 1.

ml/sq m. Of 16 patients with an increased plasma volume and a serum monoclonal globulin, 15 had a red cell volume measured simultaneously that was higher than the upper limit of the range predicted for the hematocrit; of 34 patients with a normal plasma volume, only 12 had an increased red cell volume (Fig. 2C). In two patients, the hematocrit was as much as 6 less than the lower limit predicted for the red cell volume. In 9 patients with monoclonal globulins greater than 5.5 g/dl and an increased plasma volume, serial measurements were repeated after chemotherapy had reduced the concentration by at least 50%. As indicated in Fig. 2B, reductions in abnormal protein level were associated with marked declines in plasma volume.

Serum viscosity. The serum viscosity was evaluated in 72 consecutive, previously untreated patients with serum monoclonal gammopathy due to myeloma (63 patients) or macroglobulinemia (9 patients). Results were compared with studies in normal volunteers, myeloma patients with only Bence Jones protein, and patients with anemia from other causes in whom the serum viscosity ranged from 1.4 to 2.0. An elevated serum viscosity was confirmed in 78% of the patients with multiple myeloma. Only 14 myeloma patients (22%) had a viscosity index greater than 3.0, and only three (5%) showed an index greater than 4.0 (two of IgG type, one of IgA type). No patient had symptoms of hyperviscosity. For a specific concentration of myeloma globulin, the mean serum viscosity was highest in patients with IgM globulins and lowest in patients with abnormal IgG proteins. While the viscosity for sera with monoclonal IgM proteins of a specific concentration was significantly higher than that for sera with IgG or IgA globulins ($p < 0.01$), the difference between sera with increased IgA and IgG proteins was not significant ($p > 0.3$). In no patient with macroglobulinemia did the calculated whole blood viscosity exceed 6.5 centipoises using the formula proposed by Mannik.¹⁰ An increased serum viscosity was usually associated with an increased concentration of myeloma globulin so

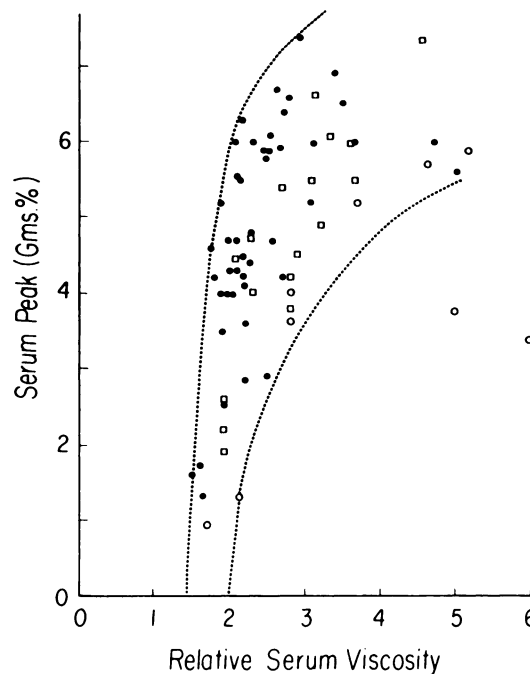


Fig. 3. Correlation between the magnitude of the serum monoclonal component and relative serum viscosity. Data from patients with abnormal globulins of IgG (●), IgA (□), and IgM (○) types are compared. Dotted lines include the ranges for all measurements except for two patients with macroglobulinemia.

that a viscosity index greater than 3.0 was confirmed in 14 patients with an IgG or IgA level greater than 4 g/dl, but in none with a lower serum concentration (Fig. 3). Two patients with IgM globulins had a viscosity index greater than 5.0, despite a serum concentration less than 4.0 g/dl.

DISCUSSION

Numerous hematologic disorders have been associated with abnormalities in red cell volume, plasma volume, or both. This report presents the results of blood volume studies in a large number of patients with chronic anemia and monoclonal gammopathies. Individuals with splenomegaly or other known causes for an increased plasma volume were excluded. Standard isotope procedures were used; results were expressed in terms of the body surface area; and both men and women were combined in the analyses. Since an elevated plasma volume may occur with anemia from any cause, increased values were defined by elevations greater than expected for a specific hematocrit; an elevated total blood volume was confirmed when the combined red cell and plasma volumes exceeded the highest value identified in our control population.

In the anemic patients without serum monoclonal globulins or splenomegaly who were studied, there was a linear and predictable relationship between the hematocrit and red cell volume. For patients with a hematocrit less than 40, the red cell volume was predictable within 20% of the measured value. Huber et al. defined the close relationship between venous hematocrit and red cell volume in normal and anemic subjects and found that only patients with a disproportionate increase in plasma volume due to certain medical disorders showed any deviation.⁴ Thus the red cell volume can be deduced from the

hematocrit in the absence of clinical disorders known to affect plasma volume.¹⁻⁷ With erythrocytosis, the red cell volume increased more markedly than predicted from increments in the venous hematocrit. This observation was also noted by others,^{4,5} and was attributed to the normal plasma volume in most patients with a high hematocrit.⁶ The total body hematocrit is the ratio of the red cell mass to the sum of the red cell mass and plasma volume; thus, a specific increase in a high red cell volume would elevate the hematocrit less than the same number of red cells added to a low red cell volume.

A large fraction of patients with serum monoclonal proteins due to myeloma or macroglobulinemia had an increased plasma volume and total blood volume. A falsely elevated plasma volume may have resulted from a rapid loss of radioactive albumin to the extravascular space during the isotope procedure because of increased capillary permeability or a decreased serum albumin pool. Since the measured red cell volume was also higher than predicted for the hematocrit in the same patients considered to have an increased plasma volume, this possibility was unlikely.

An increased plasma volume has been well documented in patients with macroglobulinemia, where the danger of transfusing patients with hypervolemia has been emphasized.^{7,11} Similar observations have been described in isolated patients with myeloma.^{11,12} This report documents that a large fraction of myeloma patients with a serum protein abnormality have an increased plasma volume and total blood volume. Thus, some of the apparent "anemia" in many patients with serum monoclonal gammopathy results from an expanded plasma volume, which produces a measured venous hematocrit as much as 6 lower than that predicted from the red cell volume. Direct measurements of the red cell volume in patients with serum protein abnormalities, and a low hematocrit will spare many the need for unnecessary and potentially hazardous red cell transfusions. Demonstration of an increased plasma volume, using more rapid and convenient isotope procedures, may also explain a low hematocrit. In patients with macroglobulinemia, assessments of plasma volume also provide a more rational basis for plasmapheresis.

The hyperviscosity syndrome has been described in many patients with Waldenström's macroglobulinemia, as well as in some with multiple myeloma. MacKenzie et al. have demonstrated that serum viscosity values greater than 6.0, and IgM concentrations greater than 4 g/dl are usually necessary before symptoms occur.^{7,13} Marked increases in serum viscosity may occur with low IgM levels, and only slight increases in viscosity may occur with high IgM levels. The absence of clinical evidence of hyperviscosity in our study was attributed to the low concentration of IgM globulin present in most of our patients who usually had been referred for the evaluation of an overt lymphoma or chronic lymphocytic leukemia. Since hyperviscosity complications may occur with low concentrations of IgM globulins, the serum viscosity and plasma volume should be determined in all patients with IgM peaks.

Serum hyperviscosity of slight degree occurred in most of our myeloma patients with monoclonal serum globulins, but none showed any clinical manifestations from this abnormality. Similar magnitudes of hyperviscosity have been described in other patients with multiple myeloma.¹⁴⁻¹⁷ In one series, pro-

teins with an IgG₃ subclass were present in about one-half of the IgG patients with hyperviscosity.¹⁵ For similar protein levels, the serum viscosity was higher when IgA, rather than IgG, globulins, were present; this was attributed to the higher molecular weight and the greater tendency of IgA molecules to form polymers. Since serum hyperviscosity has been reported only when abnormal IgG or IgA proteins exceeded 5.0 g/dl,¹⁴⁻¹⁷ serum viscosity measurements are indicated in myeloma patients only when monoclonal globulins are greater than this level.

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