THE INFLUENCE OF FIBRINOGEN AND OTHER PLASMA PROTEINS ON THE ESR AND PLASMA VISCOSITY

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INTRODUCTION

The erythrocyte sedimentation rate (ESR) is one of the commonest clinical tests used to screen for the presence of a disease state or to follow up its activity. It is a standard test for monitoring inflammatory disease processes. However, factors unrelated to the presence or absence of inflammation may limit its usefulness. This is often the case in chronic renal disease where the ESR may be persistently elevated.[1,2]

It is generally agreed that the ESR depends primarily, though not exclusively, on the concentration, of asymmetric marcomolecules, primarily fibrinogen and gamma globulins, and on the concentration of erythrocytes in plasma. Since the concentration of fibrinogen and globulins are commonly elevated in inflammatory disease, the ESR is used as a screening test for the presence of infections particularly chronic infection, or to monitor the progress of chronic inflammatory processes such as rheumatoid arthritis. The ESR also depends on the red cell shape and number, hence it is better in certain special conditions to directly measure plasma viscosity which is a function of plasma protein content.

Changes in the plasma viscosity can only be due to changes in the plasma itself. The most important factor influencing plasma viscosity are the plasma proteins, of which fibrinogen is the most important. Gamma globulins may influence plasma viscosity significantly especially in situations where there is an excess of a monoclonal protein as in multiple myeloma.

The present study was undertaken to determine the influence of fibrinogen and other plasma proteins on the ESR and plasma viscosity in patients with various chronic disorders. Both these parameters are expected to vary with the plasma protein concentration, as described by Hutchison and Eastham.[3] It is also intended to ascertain if ESR determination is adequate in certain conditions to access disease activity, or whether viscosity measurement would be more appropriate. Changes in one other acute-phase protein, C-reactive protein (CRP), are also observed. Measurements of the zeta sedimentation ratio (ZSR) were also made on all the samples.

MATERIALS AND METHODS

For this preliminary study, the patients were those admitted to the various wards in the General

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Hospital, Kuala Lumpur. In addition to the routine history and physical examination, all the patients had the following tests: plasma viscosity, fibrinogen level, total serum protein, albumin, C-reactive protein (CRP), zeta sedimentation ratio (ZSR) and erythrocyte sedimentation rate (ESR). Only patients who gave their consent were used in this study.

Control groups of male and female were from the staffs and trainees of the Institute for Medical Research, Kuala Lumpur.

A total of 88 patients were studied, their age ranging from 9 to 82 with a mean of 43 years. The control groups were made up of healthy males and females, their ages ranging from 19 to 35 with a mean of 22 years.

The ESR was obtained using the classical Westergren technique. Plasma viscosity was measured by a viscometer from Coulter Electronics, measurement being made at 37°C using the method of Harkness.[4] The method for ZSR was modified from Bull and Douglas.[5] Fibrinogen levels were determined using a method modified from Ellis and Stransky.[6] Quantitative CRP was measured by laser nephlometry according to Kindmark.[7] Total serum protein was determind by Biuret method and albumin by the dye-binding method.[8]

RESULTS

The normal range, taken as the mean plus/minus two standard deviations, for the various tests done in this study are given in Table I. No previous report has been made on the normal range of these tests amongst the Malaysian population.

For the group of 88 patients, the influence of fibrinogen and various plasma proteins on the ESR and plasma viscosity were evaluated by statistical analysis. The various correlations between fibrinogen and other plasma proteins with ESR and plasma viscosity are shown in Table II. Plots which provide more information about the relationship between these variables

TABLE I
NORMAL RANGE OF TESTS USED IN THE STUDY

Test	n	Normal Range (mean ± 2 SD)
Total serum protein	48	(77 ± 8) gm/l
C-reactive protein	44	(6.6 ± 6.7) mg/l
Plasma viscosity	37	(1.3 ± 0.2) centipoise (cps)
Fibrinogen	42	(2.8 ± 1.2) gm/l
ESR	34	(9.3 ± 17) mm/hr
ZSR	37	(40 ± 4.8) %
Albumin	48	(48 ± 6) gm/l
Gamma globulin	48	(29 ± 2) gm/l

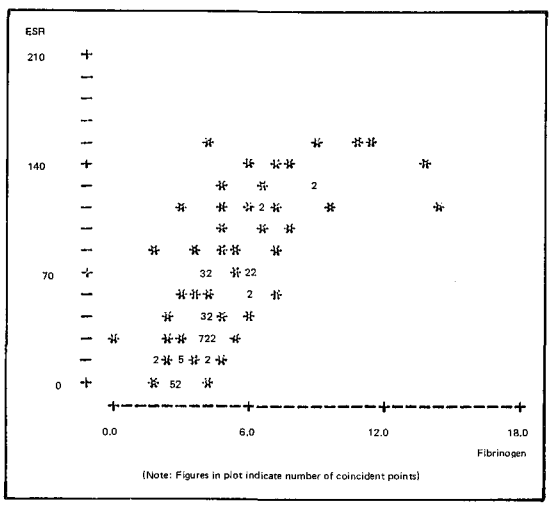

Fig. 1 Plot showing the relationship between ESR and fibrinogen.

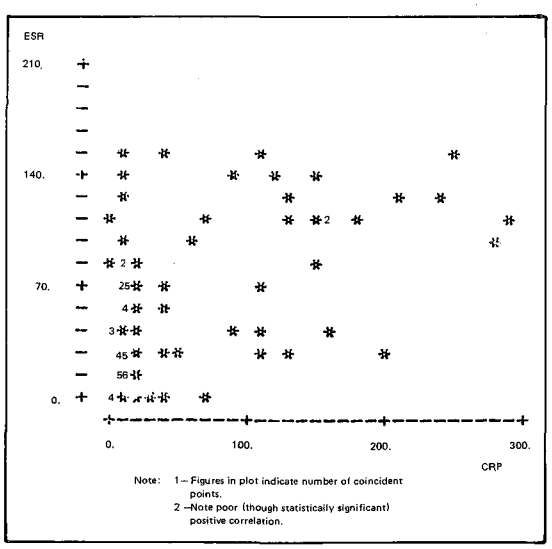

Fig. 2 Plot showing the relationship between ESR and CRP.

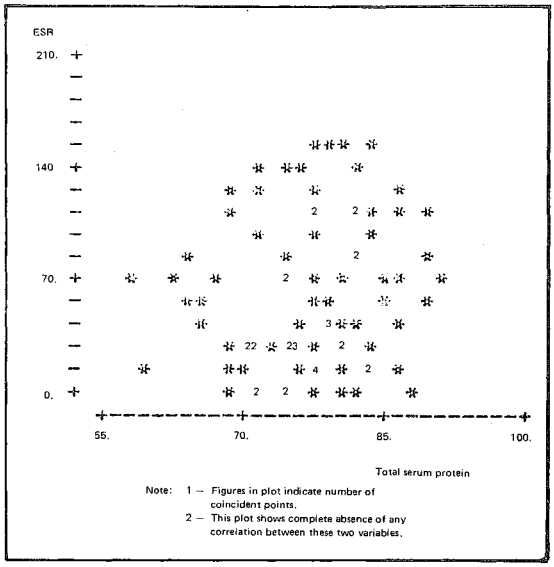

Fig. 3 Plot showing the relationship between ESR and total serum protein.

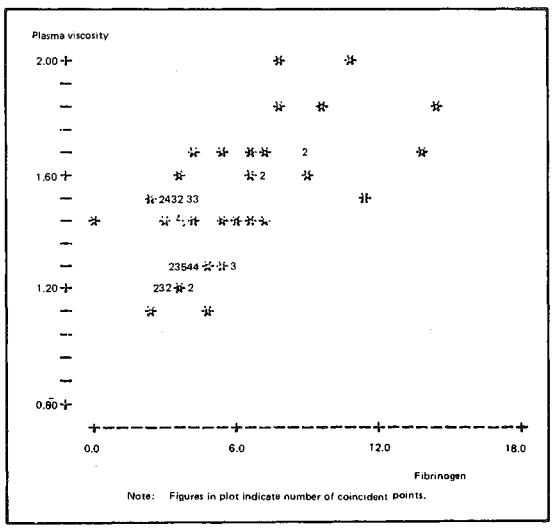

Fig. 4 Plot showing the relationship between plasma viscosity and fibrinogen.

are given in Figures 1–5. From these figures, it is clear that the variables are linearly related to different degrees with the exception that albumin is neither positively correlated to ESR, showing a negative influence over its value; nor is it in any way correlated to plasma viscosity. There are no outlying points which might have

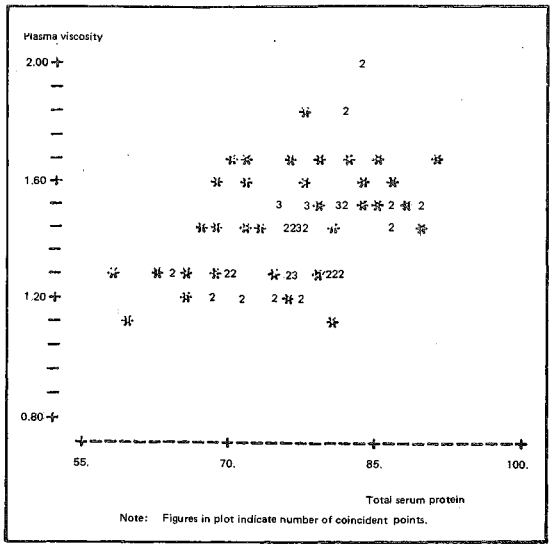

Fig. 5 Plot showing the relationship between plasma viscosity and total serum protein.

TABLE II
CORRELATIONS BETWEEN FIBRINOGEN AND VARIOUS PLASMA PROTEINS AGAINST ESR AND PLASMA VISCOSITY

Independent variable	Dependent variable	n	Correlation value, r	p value
CRP	ESR	88	0.5280	<0.001
Fibrinogen	ESR	88	0.7144	<0.001
Total serum protein	ESR	88	0.1217	ns
Gamma globulin	ESR	88	0.5210	<0.001
Albumin	ESR	88	–0.4010	<0.001
Plasma viscosity	ESR	88	0.6534	<0.001
ZSR	ESR	88	0.5601	<0.001
CRP	Plasma viscosity	88	0.4689	<0.001
Fibrinogen	Plasma viscosity	88	0.4760	<0.001
Total serum protein	Plasma viscosity	88	0.4133	<0.001
Gamma globulin	Plasma viscosity	88	0.5226	<0.001
Albumin	Plasma viscosity	88	–0.1313	ns

influenced the results in those cases where a positive correlation exists.

The correlations between the ZSR and fibrinogen levels and those of other plasma proteins are shown in Table III. There were significant positive correlations in all cases except between total serum protein and ZSR. Again, as shown in Table III albumin alone has a negative influence over the ZSR value. The plots of ZSR against fibrinogen and other plasma proteins are very similar to those given in Figures 1–3.

TABLE III
CORRELATIONS BETWEEN FIBRINOGEN AND VARIOUS PLASMA PROTEINS WITH ZSR

Independent variable	Dependent variable	n	Correlation value, r	p value
Fibrinogen	ZSR	88	0.4262	<0.001
Total serum protein	ZSR	88	0.1508	ns
Gamma globulin	ZSR	88	0.4324	<0.001
Albumin	ZSR	88	−0.2605	<0.005
Plasma viscosity	ZSR	88	0.4967	<0.001
CRP	ZSR	88	0.3319	<0.005

DISCUSSION

The ESR has, for many years, been used as a non-specific indicator for the presence of inflammation. Elevation in the ESR is the result, in large measure, of the presence of asymmetric macromolecular proteins that enhance red cell rouleaux formation, fibrinogen being the most important of these proteins.

In this study, the correlation analysis done verified the influence of fibrinogen on both the ESR and plasma viscosity measurements.

In other studies, increase in gamma globulins has been well established to cause an increase in both ESR and plasma viscosity measurements.[4,9]

In our study, we did not find evidence of a relationship between total serum protein with either ESR or ZSR, but a significant correlation was seen in our study between total serum protein and plasma viscosity measurement. However, gamma globulins showed significant positive correlations with ESR, ZSR and plasma viscosity measurements, whereas albumin alone affected these three tests in the opposite direction. This finding is similar to the observation made by Hutchison and Eastham.[3]

C-reactive protein measurement is useful as an index of infections and inflammation. When measured quantitatively, the CRP levels appear to be a sensitive indicator of underlying inflammatory disorder.[9] It is an acute-phase protein that can be directly measured using immunochemical techniques. A previous study by Anthony *et al.*,[10] showed that CRP measurements in patients with infectious inflammation undergoing continuous ambulatory pertioneal dialysis (CAPD) is a better index than ESR. In this study, the CRP changes in parallel with ESR but the correlation, although significant, is poor.

The ZSR is a measurement similar to the ESR but possesses several advantages. It is unaffected by anaemia and responds in a linear manner to increase in fibrinogen and/or gamma globulins. The ZSR was measured in this study to evaluate its usefulness and the possibility of it replacing ESR due to the advantages it has. The results obtained showed a significant correlation between ZSR and ESR ($r = 0.5601$, $p < 0.001$).

Plasma viscosity and fibrinogen also showed some influence on the measurements of ZSR in this study. Since ZSR is not affected by anaemia, uses less blood and a shorter time for carrying out the test, it would be a useful alternative to ESR in the investigation of diseases involving changes in plasma proteins with concurrent anaemia or polycythemia.

It would appear that in most clinical situations the ESR and plasma viscosity are both increased in parallel with the changes in fibrinogen levels. However, this study indicates that plasma viscosity changes may take place in response to changes in serum protein alone, whereas changes in serum protein alone do not seem to influence the ESR, which is more directly influenced by fibrinogen and globulin levels.

Since albumin counteract the rouleaux-forming properties of macromolecular proteins,[3] normal or increased albumin concentrations will decrease rouleaux formation, while conversely hypoalbuminaemia will increase the sedimentation rate even when the macromolecular proteins are normal. In practice there must be very few clinical conditions in which both fibrinogen and total serum protein levels (mostly secondary to changes in gamma globulin levels) do not change in parallel. Such conditions however, do exist, as in myelomatosis. In these special circumstances, it is probably more appropriate to follow disease

activity with plasma viscosity measurements and not utilise the ESR which can be influenced by the changes in albumin level, known to occur commonly in these situations.

In conclusion, we suggest that the ESR is a useful screening test for the presence of an inflammatory process, since it reflects changes in fibrinogen and gamma globulin levels, but alternative measurements are available to follow disease activity when factors other than the disease itself can adversely affect the ESR value. When red cell shape and concentration are abnormal, the ZSR is a useful alternative. Plasma viscosity would be a more useful parameter to measure in situations as in myelomatosis, where one is particularly interested in the changes in plasma protein levels as a measure of disease activity; it is also important to note that the lowering in albumin level has a positive influence over the ESR, and this is not uncommon in myelomatosis as well as liver disease. Changes in serum proteins secondary to the disease can occur in protein losing nephropathy or enteropathy; here again albumin would be expected to be affected more than other plasma proteins. In these situations again, the ESR would be an unreliable indicator of disease activity and it would be better to measure the changes in a particular acute-phase protein like the C-reactive protein in these circumstances.

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