Blood hyperviscosity with reduced skin blood flow in scleroderma

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SUMMARY The vascular complications of scleroderma have previously been attributed to the progressive obliteration of small vessels. Our study was carried out to determine whether abnormalities of blood viscosity occur in this disease, thereby contributing to the ischaemic process. Blood viscosity was measured in 20 patients using a rotational viscometer. At a high rate of shear, blood hyperviscosity was found in 35% of the patients and at a low rate of shear, in 70%. In addition there was a significant increase in the plasma viscosity which implicates changes in plasma proteins (fibrinogen, immunoglobulins) as causing the hyperviscosity. Measurement of the hand blood flow by venous occlusion plethysmography showed reduced flow at 32°, 27°, and 20°C. A unique finding was a delayed recovery of the blood flow after cooling. These observations suggest that the increased resistance to blood flow in skin affected by scleroderma may be caused by an interaction between the occlusive vascular lesion and blood hyperviscosity. In addition, blood flow patterns and hyperviscosity could help distinguish scleroderma from primary Raynaud’s disease.

In patients with scleroderma several of the clinical features, such as Raynaud’s phenomenon, can be attributed to a reduced blood flow through small arteries, arterioles, and capillaries. Histological and radiological studies have confirmed the existence of vascular abnormalities in this disease (Solà, 1964; Norton and Nardo, 1970; Rodnan, 1972; Campbell and LeRoy; 1975), although the cause of these changes is unknown. Since the resistance to blood flow is partly dependent on the blood viscosity, detailed studies were carried out to determine whether blood hyperviscosity exists in patients with scleroderma, thereby contributing to the already increased vascular resistance associated with narrowing of the vessel lumen. The degree of impairment of the skin blood flow in this group of patients was assessed by measuring hand blood flow and its response to cooling. We compared the results with those obtained in patients with other connective tissue diseases and with impaired peripheral circulation.

Diagnosis was made clinically with support from appropriate laboratory and radiological investigations. These included skin histology, serum protein and autoantibody studies, barium studies of the upper gastrointestinal tract, and oesophageal motility measurements.

The severity of clinical involvement of the hand ranged from mild oedema with Raynaud’s phenomenon to severe digital ischaemia. All vasoactive therapy was suspended at least 12 hours before the study. None of the patients were hypertensive or had undergone sympathectomy or intra-arterial therapy before the study.

Methods

Blood and Plasma Viscosity

Blood and plasma viscosities were measured using a rotational viscometer, the coaxial members of which have a rhombospheroid geometry (Dintenfass, 1969; McGrath, 1974). The speed of rotation-shear rate conversion factor was calculated from the geometry of the rhombospheroids as described elsewhere (Oka, 1960; McGrath, 1974). The instrument was calibrated using viscosity certified oils (Commonwealth Scientific and Industrial Research Organization, National Standards Laboratory, Sydney, Australia). Temperature control was...
obtained by means of a water jacket enclosing the rhombospheroids. All studies were carried out at 35°C and on blood anticoagulated with dry EDTA (1 mg/ml). The studies were completed within 3 hours of venepuncture. Blood viscosity was measured at 73 and 0.18 sec⁻¹, representing a high and low rate of shear respectively (Fig. 1), and the plasma viscosity was measured at 37 and 1.5 sec⁻¹. Technical limitations prevented the measurement of plasma viscosity at rates of shear above 37 and below 1.5 sec⁻¹.

The blood viscosity of 37 normal subjects was measured to determine the normal viscosity range for this instrument. In addition, the haematocrit was varied in 14 cases by the addition or removal of autologous plasma to permit a valid statistical analysis of the blood viscosity for haematocrits from 30 to 50%. The linear regression line and tolerance limits for P = 0.05 were calculated on logarithmic transformed viscosity data. Blood hyperviscosity is defined as a blood viscosity value which is above these tolerance limits at the given haematocrit. The distribution of ages of the normal subjects was similar to the patients with scleroderma. The plasma viscosity of 22 normal subjects was also measured.

Haematocrit was measured using heparinized microhaematocrit tubes (Sherwood). Premixed blood was drawn into the capillary tubes which were then centrifuged at 14,000 g for 5 minutes (Clements Micro-Haematocrit centrifuge). The haematocrit was read to the nearest 0.5% using the Micro Haematocrit Capillary Tube Reader (Sherwood).

**HAND BLOOD FLOW**

Hand blood flows were measured by venous occlusion plethysmography as described elsewhere (Greenfield et al., 1963; Ardill et al., 1967). The changes in hand volume were recorded directly by the displacement of air above the water of the plethysmograph to a low-inertia float volume recorder and kymograph.

Before each experiment the patient lay supine for 30 minutes in a quiet, temperature-controlled room (23°C) and all experiments were carried out under these conditions. During each experiment the temperature of the water in the plethysmograph enclosing the right hand was maintained at 32°C so that the blood flows recorded from this hand served as a continuous control. This was necessary because, on occasions, the sequential hand blood flows varied widely, apparently as the result of spontaneous changes in the peripheral sympathetic vasoconstrictor tone. These fluctuations occurred synchronously in both hands and were approximately equal on both sides (Figs. 2, 3).

Blood flow measurements were recorded from the experimental (i.e. left) hand after sequential temperature changes to 32°, 27°, 20°, and 32°C. The recordings were calibrated by the injection of known volumes of air into the tubing above the plethysmograph. The hand blood flows were calculated using the method described by Greenfield et al. (1963) and expressed as ml blood/100 ml hand tissue per minute. To arrive at an estimate of the net effect of each temperature change a correction procedure was applied which used the spontaneous fluctuations in the control hand blood flows (Duff, 1952). In addition, the hand blood flows in 15 normal adult subjects (laboratory and hospital staff) were measured. Within this group there was no significant relationship between hand blood flow and age, thus supporting conclusions reached previously (Shepherd, 1963).

Statistical analyses were performed using Student's
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Results

Blood viscosity

Normal subjects

There was a linear correlation between the log viscosity and haematocrit for the range of haematocrits from 30 to 50%. The tolerance limits for $P = 0.05$ are shown in Fig. 1. Extrapolation of the regression line to zero haematocrit (i.e. plasma) gives a viscosity of 1.27 and 3.03 centipoise (cp) for...
73 and 0.18 sec\(^{-1}\) respectively. These values agree with the normal plasma viscosity results obtained at 1.5 sec\(^{-1}\) (see below). The relationship observed between viscosity and haematocrit is similar to that reported in other studies using different types of viscometer (Wells and Merrill, 1962; Rand et al., 1964; Chien et al., 1966; Dormandy, 1970; Copley, 1973).

Scleroderma
At a shear rate of 73 sec\(^{-1}\) 7 patients (35%) had blood hyperviscosity and at 0.18 sec\(^{-1}\) there were 14 patients (70%) with hyperviscosity (Fig. 1).

PLASMA VISCOSITY
Normal subjects
Plasma viscosity at 37 sec\(^{-1}\) was 1.39 ± 0.10 cp (mean ± SD) and at 1.5 sec\(^{-1}\) was 2.60 ± 0.35 cp.

Scleroderma
Plasma viscosity in scleroderma was significantly increased (P < 0.005) above normal at both rates of shear, being 1.55 ± 0.15 cp and 4.13 ± 1.90 cp at 37 and 1.5 sec\(^{-1}\) respectively.

HAND BLOOD FLOW
Normal subjects
The hand blood flows at 32°, 27°, and 20°C were 5.99 ± 2.68 (mean ± SD), 4.73 ± 2.39, and 2.12 ± 1.90 ml blood/100 ml tissue per min respectively. Cooling of the hand from 32° to 27°C resulted in a 27.2 ± 4.6% (mean ± SE) decrease in flow, and cooling from 32° to 20° resulted in a 63.8 ± 4.6% decrease. Therefore the change in hand blood flow over this temperature range is approximately 5% per centigrade degree. After rewarming of the hand from 20° to 32°C the hand blood flow recovered to within 1.1 ± 2.2% of control (Figs. 2, 4).

Scleroderma
The hand blood flows at 32°, 27°, and 20°C were 3.29 ± 2.33 (mean ± SD), 2.20 ± 1.76, and 1.00 ± 0.75 ml blood/100 ml tissue per min respectively. These values are all significantly below (P < 0.005) the corresponding values in the normal subjects. The decreases in blood flow with cooling from 32° to 27° and from 32° to 20°C were 31.5 ± 2.7% (mean ± SE) and 66.3 ± 3.2% respectively. These values are not significantly different from the corresponding results obtained in the normal group. By contrast, the degree of recovery of the hand blood flow in scleroderma with rewarming from 20° to 32°C was only 60.5 ± 4.6%, which is significantly below (P < 0.001) the recovery in the normal group (Fig. 3, 4). For comparison, the results of blood flow changes are shown for patients with peripheral vascular disease and primary Raynaud's disease. Of all groups of diseases studied, scleroderma alone produced such a pattern of response.

Discussion
By means of a rotational viscometer it is possible to measure the viscosity of whole blood at a uniform rate of shear and hence determine accurately the intrinsic resistance to flow offered by a particular sample of blood under given conditions of flow. The instrument used in our study has the capacity to measure the blood viscosity at both high and low rates of shear and therefore the contributions of haematocrit and red cell aggregation to the blood viscosity can be determined separately. Interpretation of the results is supported by measurements of

Fig. 4 Effect of temperature on the hand blood flow in normal subjects (n = 15) and in patients with scleroderma (n = 20). The per cent change in blood flow (mean ± SE) was corrected for spontaneous fluctuations (see text). The difference between the two groups after rewarming (from 20°C to 32°C) is significant (P < 0.001). For comparison, results are included for patients with peripheral vascular disease (n = 18) and those with primary Raynaud’s disease (n = 22). Differences from scleroderma patients after rewarming are significant.
the plasma viscosity and haematocrit; an increase in
the former indicates a change in the plasma proteins
and since certain plasma proteins promote red cell
aggregation, is more likely to be associated with
blood hyperviscosity at low rates of shear; whereas
an increase in the haematocrit predisposes to blood
hyperviscosity at both high and low rates of shear
(Chien et al., 1966).

The validity of the measurements obtained with
the instrument used in the present study has pre-
viously been established by comparison of the results
obtained in a normal group of subjects with the
normal viscosity ranges reported by other investi-
gators using different viscometers (McGrath, 1974).
In addition, the presentation of data in the manner
illustrated allows a ready evaluation of the results
relative to the normal range for each given haemato-
crit. The temperature of each sample was carefully
controlled during the recordings since the viscosity
of fluids increases with decreasing temperature.

The high incidence of blood hyperviscosity found
in these patients suggests that this abnormality may
contribute significantly to the vascular complications
of scleroderma. In particular the observation that the
majority of patients had blood hyperviscosity at low
rates of shear draws attention to the high resistance
offered by the blood, especially at low flow rates.
The significant increase in the plasma viscosity, which implies that there is either an increase or a
physicochemical change in the macromolecular
components of plasma, is consistent with the
greater incidence of blood hyperviscosity at low
rates of shear.

Whether blood hyperviscosity in scleroderma is
the result of a primary haematological abnormality
or is secondary to the disease process cannot be
determined on the available evidence. Increased red
cell aggregation has been reported in association
with a variety of forms of tissue injury (Davis and
Landau, 1966; Charm and Kurland, 1972; Chien,
1975), but the mechanism of the aggregation
remains speculative. In some cases it is apparently
related to fibrinogen, in some to other plasma
proteins, and in others it has been attributed to
altered properties of the red cell surface.

Although these factors were not analysed in the
present study other investigations have confirmed
that serological abnormalities are frequent in
scleroderma and include hypergammaglobulinaemia
(Clark et al., 1971; Rodnan, 1972) and rheumatoid
factor (Clark et al., 1971; Rodnan, 1972). Such
changes are consistent with the raised erythrocyte
sedimentation rate (Clark et al., 1971) and increased
intravascular red cell aggregation (Davis and
Landau, 1966; Redisch et al., 1970) in this disease.

In our patients, raised ESR, fibrinogen, immuno-
globulins, and cryoproteins were uniformly asso-
associated with hyperviscosity. At least in para-
proteinemia a very close relationship existed
between hyperviscosity and immunoglobulin con-
centration (McGrath and Penny, 1976). However, no
clear correlation existed between disease activity,
disease extent, antinuclear antibodies, rheumatoid
factor, and hyperviscosity in scleroderma. In fact,
our data have perhaps more relevance to hyper-
viscosity being an added mechanism of ischaemia
rather than being a laboratory aid in diagnosis,
except in distinguishing Raynaud’s disease.

Hyperviscosity is present in many patients with
connective tissue diseases with comparable preval-
ence and therefore scleroderma is not separable on
these grounds. Yet it does highlight an infrequently
appreciated phenomenon in all these disorders
(McGrath, 1974). However, none of the patients
fulfilling the criteria for a diagnosis of primary
Raynaud’s disease had hyperviscosity (McGrath
et al., 1977b). Measurement of viscosity therefore
would be of considerable help in this latter clinical
situation to distinguish early scleroderma.

The abnormal blood vessels in scleroderma skin
predisposes to slow blood flows and low rates of
shear. Since the blood viscosity increases dispro-
portionally with decreasing rate of shear there
will be regions of the skin circulation in which the
viscous resistance is abnormally high. Under these
conditions local haemodynamic forces may be of
insufficient magnitude to maintain flow resulting in
stasis, vascular occlusion, and tissue ischaemia.
Although such a sequence remains speculative it is
consistent with the results of the hand blood flow
measurements and, in particular, with the ab-
normally slow recovery of the skin blood flow after
exposure to cold. The hand blood flow observations
presented in Fig. 4 are completely unique to
scleroderma. None of the disease groups analysed
showed such a defective recovery. Therefore,
scleroderma could be distinguished from SLE,
rheumatoid arthritis, and primary Raynaud’s
disease, all of which have normal flow recoveries
after cold exposure (McGrath, 1974; McGrath et al.,
1977b).

The reduced hand flow rates reflect severe
increases in the resistance to flow and confirm
previous observations that there are marked
abnormalities of the peripheral circulation in this
disease. The mechanism of the slow recovery after
cold could be a prolonged cold-induced vasoconstric-
tion or a failure of the intravascular cellular ag-
gregates formed during the cold to disperse, or to a
combination of these phenomena. Although the
precise mechanism cannot be identified from the present study the association of blood hyperviscosity suggests a causative role, at least in part, for intravascular red cell aggregation.

These observations therefore support a multifactorial basis for the frequent vascular complications of scleroderma since the coexistence of blood vessel abnormalities and blood hyperviscosity will result in a higher resistance to blood flow than either factor alone. In addition, we suggest that this combination is responsible for the progressive nature of the vascular changes in this disease.

M. A. McG. was supported by National Health and Medical Research Council of Australia Medical Postgraduate Research Fellowship.

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Ann Rheum Dis 1977 36: 569-574
doi: 10.1136/ard.36.6.569

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