Capillary Fragility Studies in Diabetes

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Summary: A new method for the measurement of capillary fragility based on the time of appearance of petechiae under standardized conditions has been used to study 88 non-diabetics and 211 patients attending a diabetic clinic. In the former the capillary fragility increased with age. In the diabetic group 78 out of 195 patients had complications, and in all age groups these latter patients had more fragile capillaries.

In general the capillary fragility was greater in patients taking insulin than in those taking antidiabetic tablets or on diet alone, and in the first group capillary fragility was greatest in those receiving more than 50 units daily and least in those receiving less than 25 units daily.

Capillary fragility measurement by this method may be of value in assessment, prognosis, and studying the response to treatment in diabetes.

Introduction

In recent years capillary abnormalities have been noted in many diseases, but the measurement of capillary fragility has been neglected as a clinical investigation, possibly because of the difficulties of the test, the available methods being time-consuming, uncomfortable for the patient, or difficult to interpret (Peck and Copley, 1946 ; Munro *et al.*, 1947). All methods of capillary fragility measurement depend on the appearance of petechiae, and this may vary with skin thickness, the site chosen, room temperature and humidity, as well as the extent and duration of the pressure applied. Also, as petechiae continue to appear after pressure has been released petechial counts are subject to considerable error.

With a standard technique it may be postulated that the number of petechiae seen at a given site depends on the pressure applied, its duration, and the capillary fragility. In the recognized methods pressure (positive or negative) and time are standardized, and a result is obtained by counting petechiae. We have devised a method for measuring the capillary fragility which does not depend on total petechial counts. It is based on the simultaneous application of positive and negative pressure. The time of appearance of a given number of petechiae is noted, and, as pressure is standardized, time is the measured variable.

Method

The apparatus is diagrammatically represented in Fig. 1. Positive pressure is applied to the forearm by means of a sphygmomanometer cuff inflated to 50 mm. of mercury. Immediately afterwards suction from a controlled source (A) is applied by a cup (C) 3 cm. in diameter and 3 cm. deep, which incorporates a lens magnifying two and a half times and a light source operated from a dry battery (D). The cup is placed on the anterior aspect of the forearm 2 to 3 in. (5 to 7·5 cm.) above the wrist skin crease, and negative pressure, measured by a manometer (B), applied to a level of 375 mm. Hg, which is reached within 10 seconds. Both pressures are kept steady and the appearance of six or more petechiae is timed. At this point the pressures are released. It has been noted that when conditions are exceptionally hot and humid apparent increased capillary fragility may be present. Blotches of redness, which disappear within an hour or two, may appear and be confused with true petechiae. In view of this care must be exercised when performing tests in hot, humid weather.

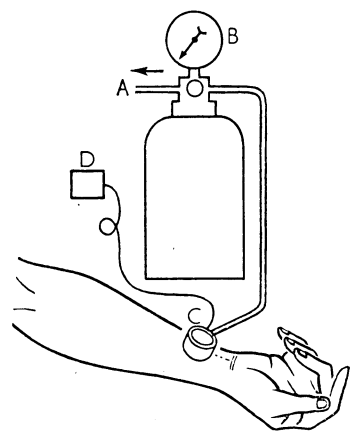

FIG. 1.—Diagram of apparatus. A, suction source ; B, vacuum gauge ; C, illuminated cup with magnified lens ; D, 6-V. power pack.

Results

Capillary Fragility in Non-diabetics

The non-diabetic group consisted of 88 subjects. They comprised 50 women and 38 men aged 20 to 76 years. Although they were not physically examined, they were all apparently in good health and not receiving any treatment. Their capillary fragility was measured by the method described, and in 15 subjects the test was repeated after three months. The results were unchanged in 12 cases, and in the remaining three the variation in the end-point did not exceed 20 seconds.

The capillary fragility results were related to the subject's age (Fig. 2). In the age groups 20 to 40 years the end-point to the test was reached within two minutes in only one subject out of 30. With increasing age the capillary fragility increased, and in the age groups 50 and over 12 out of 38 subjects developed more than six petechiae within two minutes.

Capillary Fragility in Diabetic Patients

The capillary fragility of 211 diabetic patients attending Salford Royal Hospital was measured on at least three occasions, at intervals over a two-year period. The patients comprised 117 women and 94 men. Thirty-two women were receiving insulin, 61 were taking tablets, and 24 were on diet alone. In the male group 41 were receiving insulin, 36 tablets, and 17 were on diet.

Patients were tested as the opportunity arose, and no special selection was made. However, the results presented apply only

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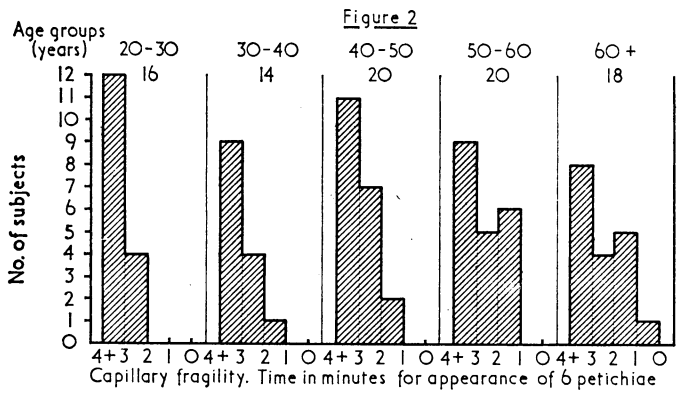
to patients who were considered to be stable diabetics, having two consecutive blood sugars of less than 300 mg./100 ml. at clinic attendance without change of treatment. Sixteen of the 211 patients were either insufficiently documented or unstable, so that their capillary fragility measurements do not appear in the results.



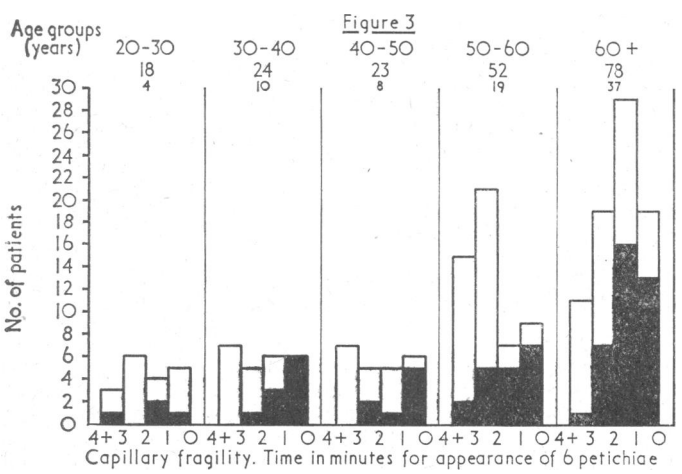


FIG. 2.—Capillary fragility in non-diabetics. FIG. 3.—Capillary fragility in 195 diabetics, 78 of whom had sequelae. □ Diabetic group. ■ Patients with sequelae.

The capillary fragility results of the remaining 195 patients are given in Fig. 3 to show the capillary fragility related to the patient's age and also to the presence or absence of retinal, renal, arterial, or neurological disease due to diabetes. Altogether 78 of the 195 patients had complications. In all age groups an increased proportion of the patients with complications had more fragile capillaries. In 59 (76%) of the 78 patients with complications the end-point of the test was reached in under two minutes. In the remaining 117 patients without complications only 37 (32%) produced six or more petechiae in the test in less than two minutes.

The Table shows the capillary fragility related to type of treatment. In general the end-point of the test was reached in a shorter time in patients taking insulin than in those taking tablets or on diet alone. This was evident despite the fact that the patients on insulin were younger than the patients in the other two groups.

Capillary Fragility Related to Type of Treatment of Diabetes

Capillary Fragility End-point	Treatment		
	Insulin	Tablets	Diet Alone
2 minutes and over	31	44	25
Under 2 minutes	42	42	11
Percentage in group with C.F. under 2 minutes	58	49	31
Mean age (years)	46	59	58

Fig. 4 shows the capillary fragility related to the insulin dose. Capillary fragility in this group was least in the patients taking less than 25 units of insulin daily and increased as the daily dose of insulin increased, so that taken as a group the patients with most fragile capillaries were those requiring more than 50 units daily.

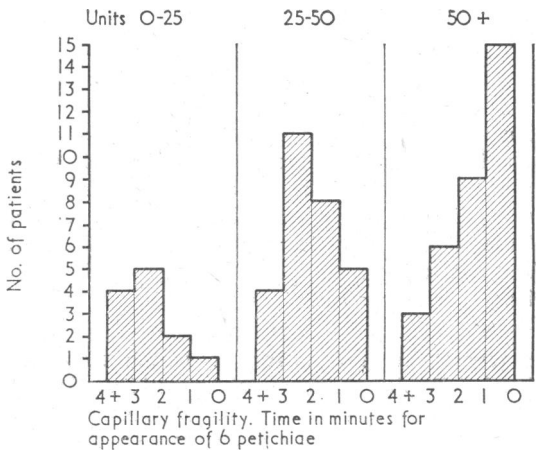


FIG. 4.—Capillary fragility related to daily insulin requirements.

Discussion

Many biological measurements vary gradually from normal to abnormal. This is exemplified by blood pressure readings, and it occurs also in capillary fragility measurements, a fact that is not made clear in descriptions of conventional methods of measuring capillary fragility. It is easy to differentiate the pathological from the undoubted normal, but difficulty arises in borderline cases. Most investigators have merely fixed an arbitrary limit of normality based on their own experience. Our results in the non-diabetic group show that the capillary fragility varies with age, a fact already observed by Bell *et al.* (1940, 1942). This means that the limits of normality should be determined for each age group, but it is uncertain whether this is a valid assumption or whether it would be better to compare all subjects with an ideal normal capillary fragility based on the results obtained in the 20 to 40 age group. We have found it necessary therefore to avoid setting limits for normality, and have compared the capillary fragility in different groups merely by the time that has been taken to reach the end-point, which is the appearance of six or more petechiae, in the standard conditions of the test.

When comparing our results in the diabetic and non-diabetic groups it is apparent that in diabetic patients the capillary fragility is in general increased in each age group. This is particularly apparent in the younger age groups. Almost all the young diabetics were treated with insulin, and, as is shown in Fig. 3, many of these patients developed petechiae within one or two minutes. We have confirmed, therefore, that in general the capillary fragility is increased in patients with diabetes, as was observed by Rodriguez and Root (1948), Barnes (1950), and Lundbæk (1953). Nevertheless, the proportion of the patients with fragile capillaries who also have complications of diabetes is striking, as shown in Fig. 3, and our results indicate that a major factor in the overall incidence of increased capillary fragility in diabetics is the presence of patients with diabetic complications in the group.

When the type of treatment is considered it is evident that patients on insulin have the greatest incidence of increased capillary fragility compared with patients taking tablets or diet alone. The differences shown in the Table are not great, but the results are more significant than they appear, as the patients taking tablets or diet were older than in the group receiving

insulin. There is also a striking difference between patients receiving a small dose of insulin and those on large doses.

The major problem in the management of diabetes is the prevention of complications. It is accepted that diabetic retinopathy and renal diseases are due to capillary damage in the retina and glomerulus respectively. It is difficult to imagine that the capillaries of the retina and kidney have been selectively damaged, and there is a growing tendency to regard these changes as part of a generalized microangiopathy of the type that one would expect as part of a metabolic disorder such as diabetes. If this were so, then capillary changes should be observed in all parts of the body, including skin and muscle, and there is a considerable amount of evidence to support this view. Thus it should be possible to use the skin capillaries as a measure of capillary damage throughout the body.

It is not possible to state at this stage whether the measurement of capillary fragility is a test of capillary pathology, though this is a reasonable assumption. Evidence in favour of this assumption is the association between increased capillary fragility and the complications of diabetes (Handelsman *et al.*, 1952; *British Medical Journal*, 1965; Moore and Frew, 1965) and the decrease in capillary fragility after hypophysectomy for diabetic retinopathy (Christensen, 1968). A direct consequence of this is that the measurement of capillary fragility offers an indication by which we may be able to select those patients who are going to develop retinopathy or other complications, but, more important, by studying the effect of changes in the diabetic state on the capillary fragility it may be possible to identify those factors which are responsible for the development of microangiopathy. Thus it seems that patients requiring large doses of insulin have increased capillary fragility, and it is interesting to speculate about a possible link between an insulin antagonist and microangiopathy.

The usefulness of capillary fragility measurement remains to be evaluated. It may be a non-specific test, as capillary abnormality is a feature of many diseases. Nevertheless, even as a non-specific test it may be of value in following a patient's progress and possibly assessing the prognosis and response to treatment. Our method is well suited to large-scale surveys and clinic screening procedures. It is quick, painless, repeatable, and over 1,500 estimations have been made in two years.

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REFERENCES

Barnes, R. H. (1950). *American Journal of Medical Science*, **219**, 368.
Bell, G. H., Lazarus, S., and Munro, H. N. (1940). *Lancet*, **2**, 155.
Bell, G. H., Lazarus, S., Munro, H. N., and Scarborough, H. (1942). *Lancet*, **2**, 536.
British Medical Journal, 1965, **2**, 603.
Christensen, N. J. (1968). *Lancet*, **2**, 1270.
Handelsman, M. B., Levitt, L. M., and Conrad, H. (1952). *American Journal of Medical Science*, **224**, 34.
Lundbæk, K. (1953). *Long-term Diabetes*. Copenhagen, Munksgaard.
Moore, J. M., and Frew, I. D. O. (1965). *British Medical Journal*, **2**, 19.
Munro, H. N., Lazarus, S., and Bell, G. H. (1947). *Nutrition Abstracts and Reviews*, **17**, 291.
Peck, S. M., and Copley, A. L. (1946). *New England Journal of Medicine*, **235**, 900.
Rodriguez, R., and Root, H. F. (1948). *New England Journal of Medicine*, **238**, 391.

Measurement of Glomerular Filtration Rate by Inulin Clearance without Urine Collection

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Summary: A continuous infusion method for measuring inulin clearance (and hence glomerular filtration rate) which does not require urine collection has been re-evaluated and found to give satisfactory results. In two non-oedematous and anephric patients the plasma level of inulin became virtually constant four hours after a single intravenous dose, and hence this is the minimum time required for the infusion with this method.

Introduction

Although inulin clearance is generally accepted as the standard method for measurement of glomerular filtration rate the method is beset by three main problems. Firstly, there is the problem of getting accurately timed urine collections without recourse to catheterization, which is often an unjustifiable hazard in the human subject. This problem was overcome by Earle and Berliner (1946) and Berger *et al.* (1948), who pointed out that if a substance was secreted from the extracellular fluid solely via the kidneys, and if the plasma level was constant, then the rate of renal excretion must equal the rate of infusion, and that the term "uv" in the classical clearance equation uv/p could be replaced by "rate of infusion/P." These authors suggested that such a method was suitable provided that renal function was reasonably good and provided that there was no oedema. Robson *et al.* (1950) pointed out, however, that a constant plasma inulin level did not necessarily mean that full equilibration had been achieved, and possibly this theoretical objection has prevented the more widespread use of this attractive technique. In order to study this theoretical objection, two anephric patients have been given single intravenous doses of inulin and the times taken for plasma inulin levels to become constant have been observed. These results are now reported, together with a further comparison of the classical and the "urineless" inulin clearance methods.

The second problem with inulin concerns its chemical measurement in plasma and urine. Times of hydrolysis and colour development must be carefully controlled in order to obtain reproducible results. The application of a Technicon

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