CAPILLARY RESISTANCE TO SUCTION IN HYPERTENSION

BY

K. R. GOUGH,* M.D., M.R.C.P.

Department of Medicine, Bristol Royal Infirmary

In hypertensive vascular disease much attention has been directed towards the lesions in the large blood-vessels, the arteries, and the arterioles. Abnormalities of these vessels, however, do not explain all the clinical manifestations that may arise, particularly in the malignant phase of the disease. Little is known of the rôle of the small vessels, the terminal arterioles, capillaries, and venules in this condition.

Attempts have been made to devise experimental techniques to measure functional changes in the capillaries of hypertensive patients. One of these is the capillary "fragility" or capillary "resistance" test. Such tests have been used in clinical medicine for more than fifty years but have fallen into disrepute because it is still uncertain that a function of the capillary is, in fact, being measured. Furthermore, numerous anatomical, physiological, and environmental factors are known to affect the result in both health and disease. Many of these variable factors are eliminated in the method used in this investigation. Results are presented in 240 normal controls and in 234 patients with hypertension, grouped according to the appearances of their optic fundi.

Method

The negative-pressure method of determining capillary resistance was used (Hecht, 1907) and the apparatus is illustrated in Fig. 1. The two-way tap (T_2) permits a measured amount of negative pressure to be admitted to the skin for 30 seconds. Standard conditions for viewing the skin are obtained by a lens built into the roof of the suction chamber, with a constant source of illumination. If gross petechial haemorrhage is produced by the level of pressure initially selected, serial reductions are then made on adjacent areas of skin until from one to three petechiae are produced in 30 seconds. The pressure at this point is recorded and is taken as the capillary "resistance."

The interscapular area of the back was used because the properties of the skin—the thickness of the epidermis, amount of subcutaneous fat, and distribution of cutaneous blood vessels—are reasonably constant over a wide area. This enables a large number of determinations to be done on skin of a constant composition at one time and also allows them to be repeated daily without waiting for petechiae to fade. The area also bears a constant relationship to the right atrium and hence variations of hydrostatic venous pressure are eliminated.

Material

Control Subjects

A total of 280 subjects (140 males and 140 females) were examined. Strict criteria for the selection of normal controls were prepared. All hospital patients

were excluded. Volunteers who were in good health and who had no history of previous disease were selected. All subjects with a diastolic blood-pressure of 100 mm. Hg or over, irrespective of age, and those with glycosuria were excluded. In females, tests were not done during menstruation because low values of capillary resistance are known to occur at this time (Brewer, 1938).

Control subjects under the age of 60 were all volunteers from the staff of the hospital and were assumed to be taking a normal diet. A careful dietary history showed that those aged 60 and over were taking adequate protein and vitamin C.

FIG. 1.—Diagram of apparatus. A=Reservoir. B=Syringe. C=Suction chamber. D=Mercury manometer. T_1 , T_2 =Two-way taps. V=Needle valve.

Hypertensive Patients

A total of 234 patients (115 males and 119 females) with hypertension were examined. The blood-pressure was recorded at least twice with the patient at rest for a minimum of 10 minutes, and the essential criterion for inclusion was the finding of a diastolic blood-pressure of at least 100 mm. Hg on each occasion. No allowance was made for arm circumference. Patients with evidence of any other disease were excluded from the investigation. Those with symptoms or signs of cardiac failure were excluded because of the possible effects of a raised venous pressure on capillary resistance, and those with a blood urea above 80 mg./100 ml. were omitted because of the bleeding tendency in uraemia.

*Ernest Hart Memorial Scholar (1958), B.M.A.

The patients were divided into three groups according to the appearance of the optic fundi:

Group 1.—This group consisted of 161 patients (69 males aged 20–86 years and 92 females aged 27–77) with “symptomless” hypertension whose ocular fundi were either completely normal or showed vascular changes only. The latter consisted of a variation or generalized reduction in calibre of the arteries and arterioles, arteriovenous nipping, or an increase in the light reflex.

Group 2.—This group consisted of 49 patients (29 males aged 35–67 and 20 females aged 43–69) with exudates and/or haemorrhages, but without papilloedema. It is appreciated that this group contains patients with “benign arteriosclerotic retinopathy” described by Foster Moore (1917) as well as the more sinister form designated “hypertensive neuroretinopathy” by Fishberg and Oppenheimer (1930). Pickering (1955) stressed that these two forms carry quite different prognoses and should therefore be distinguished wherever possible. In the absence of papilloedema this differentiation is sometimes difficult, especially when the retinopathy is bilateral and not obviously of a focal nature. It was therefore decided to include both types of retinopathy in this group.

Group 3.—This group consisted of 24 patients (17 males aged 22–61 and 7 females aged 34–54) with hypertensive neuroretinopathy and papilloedema.

The range and mean values of diastolic blood-pressure for the three groups of patients are shown in the Table.

Group	No. of Patients	Range of Diastolic Blood-pressure (mm. Hg)	Mean Value
1	161	100–160	115
2	49	100–160	128
3	24	120–160	135

Results

Control Subjects

Fig. 2 shows the results for males and females. Both sexes show a well-marked decline in capillary resistance with age. Analysis of the plotted regression lines shows that there is no significant difference between the sexes, either in the rate of change with age or in absolute levels at a given age. Age is then an important factor in evaluating any estimation of capillary resistance by this method.

Further experiments were carried out on three normal males to test the day-to-day reproducibility of results and to examine any diurnal variation. A 24-year-old subject was examined on 42 consecutive days. The range of recordings obtained was 350–420 mm. The standard deviation was 16.2 mm., the mean value 382, and the standard error ± 2.5 mm. Two subjects aged 36 and 24 were examined daily for 14 days at 9 a.m. and 6 p.m. The average difference between morning and evening values in the first subject was 11.4 mm., which is significantly different only at the 5% level of probability ($t=2.51$, $P<0.05$). The average difference in the second subject was only 2.9 mm., which is not significant ($t=0.62$, $P<0.5$). The day-to-day variation in results is thus at least as great as any diurnal variation that could be demonstrated, and for this reason readings were not restricted to a definite time of the day.

Patients with Hypertension

Fig. 3 shows the common regression lines calculated for the three groups of patients with hypertension and the normal controls. The results for males and females are shown plotted as one common regression line both for controls and for the three groups of hypertensive patients because a statistical analysis showed that there was no significant difference in capillary resistance

FIG. 2.—Capillary resistance in normal control subjects. Each point represents the value of capillary resistance obtained for each subject. The regression line represents the average rate of change with age, and from it the average value of capillary resistance for a given age may be calculated. Equations of regression lines shown plotted:—males: capillary resistance = $491 - (4.5 \times \text{age})$ (mm.); females: capillary resistance = $466 - (4.1 \times \text{age})$. Statistical analysis of these regression lines shows that there is no significant difference either in absolute value of capillary resistance or the rate of change with age. This permitted the calculation of a common regression line for normal controls, and this line is shown plotted in Fig. 3.

between the sexes at any given age. The patients with "symptomless" hypertension have very similar levels of capillary resistance to normal subjects. Patients with retinopathy, and particularly those with papilloedema, however, have significantly lower levels of capillary resistance.

FIG. 3.—Capillary resistance in the three groups of hypertensive patients compared with normal controls. Each line represents the common regression line calculated for the two sexes. Equations of regression lines: normal controls, capillary resistance = $480 - (4.3 \times \text{age})$; group 1, capillary resistance = $451 - (4.17 \times \text{age})$; group 2, capillary resistance = $320 - (3.2 \times \text{age})$; and group 3, capillary resistance = $165 - (1.1 \times \text{age})$.

Effect of Level of Diastolic Blood-pressure on Capillary Resistance

The Table shows that patients with retinopathy and those with papilloedema tend to have higher diastolic blood-pressures than those without any form of retinopathy. Since capillary resistance, measured by the technique used in this investigation, has been shown to vary with age, evaluation of any relationship with diastolic blood-pressure must be made on patients of approximately the same age. Age-group 40–49 was selected for comparison, and Fig. 4 shows the results in the three groups of hypertensive patients.

There is no direct relationship between capillary resistance and the diastolic blood-pressure. In each of the three groups, considered separately, the higher levels of diastolic blood-pressure are not regularly associated with the lowest levels of capillary resistance. However, patients in group 3 have higher diastolic blood-pressure than those in group 1, and their values of capillary

resistance are consistently lower. Patients in group 2 occupy an intermediate position. Thus there is some relationship between the highest diastolic blood-pressures and low capillary resistance.

Discussion

The limitations of this method of investigation are well recognized. Although a numerical result is obtained, the exact pressure applied to the vessel walls during exposure of the skin to suction is unknown. Furthermore, when petechiae are produced it is uncertain from which part of the peripheral vascular bed they originate. The source has been thought to be the arterioles (Rossman, 1940), the arteriolar end of the capillary loop (Humble, 1949), the tip of the capillary (Davis, 1946), and the small collecting venules (Lee and Lee, 1947). These observations, however, are not strictly comparable, since each of the authors was describing petechiae produced under different conditions, and using different techniques. It is clear that any part of the peripheral vessels may be the source of the haemorrhage in a positive test, the exact site perhaps depending upon the disease being investigated. In spite of technical objections, a comparison between normal subjects and groups of patients with hypertension is felt to be justified, particularly as gross differences have been found.

In normal subjects a well-marked decrease in capillary resistance with age has been demonstrated. This conflicts with the conclusions of Anderson *et al.* (1936), who found no change with age. Other authors have not considered the influence of age when presenting results obtained in various diseases (Bell *et al.*, 1942; Robson and Duthie, 1950). More recently, however, Brueschke (1955) and Holmgren (1957) have reported some fall of capillary resistance with age. Loss of support for the vessels from the surrounding connective tissues of the skin is a possible cause for this progressive fall with age. Keech (1958) studied changes in the morphology of human skin with age, and found a definite decrease in the amount of amorphous ground substance and increasing width of collagen fibres. The reduction in the ground substance, which normally provides the skin with a "rubber cushion" effect, may deprive the blood-vessels of some support when negative pressure is applied.

Several groups of investigators have measured capillary resistance in patients with hypertension, and some have reported low values (Griffith and Lindauer,

FIG. 4.—Relationship between diastolic blood-pressure and capillary resistance in patients aged 40–49. There is no direct relationship between diastolic blood-pressure and capillary resistance—i.e., high diastolic pressures are not always associated with low levels of capillary resistance and retinopathy.

1944; Schweppe *et al.*, 1948; Soloff and Bello, 1948). No correlation of results with clinical features, however, has been attempted. Analysis of the results in this investigation has shown that the capillary resistance in hypertensive patients without retinopathy is similar to that of normal subjects of comparable age. In patients with retinopathy, and particularly those with neuroretinopathy and papilloedema, petechiae are regularly produced with smaller amounts of suction—that is, their capillary resistance is much lower.

High arterial blood-pressure *per se* is not responsible directly for the low capillary resistance in these patients, since many of the patients in group 1 had diastolic pressures as high as those in groups 2 and 3. The reason for the low values of capillary resistance is unknown, but it may be related to structural or functional changes in the small blood-vessels, secondary to the high arterial pressure. Support for structural abnormalities in the capillaries of hypertensive patients is found in the work of Lack *et al.* (1949) and Lee and Holze (1951). They reported electron microscopy studies of capillaries in the bulbar conjunctiva of hypertensive patients and found "extensive narrowing, elongation and looping, and loss of distensibility." These authors, however, made no correlation with retinal appearances. That lesions in the capillaries may be primary and not secondary to arteriolar changes is suggested by the work of Scheinker (1948). He described post-mortem studies on the brains of patients with hypertension known to be of recent onset and found the cerebral vascular lesions to be confined to the capillaries.

Functional abnormalities in the small blood-vessels of the finger have been shown to occur in patients with hypertensive retinopathy (Coles and Gough, 1960). Observations were made on the same three groups of patients with hypertension used in the present investigation. The "critical closing pressure" of the blood-vessels of the finger was found to be lower than normal in the patients with retinopathy and papilloedema—that is, groups 2 and 3. Thus the same patients have been shown to have diminished reactivity of blood-vessels in the finger and a low level of capillary resistance in the skin of the back.

It is tempting to suggest that generalized functional changes in the small blood-vessels occur in hypertensive patients when the disease passes from the benign to the malignant phase.

Summary

A negative-pressure method of measuring capillary resistance has been described in normal subjects and in three groups of patients with hypertension, divided on the basis of retinal appearances: group 1, vascular changes only; group 2, haemorrhages and/or exudates; and group 3, neuroretinopathy and papilloedema.

The capillary resistance of normal subjects has been shown to diminish with age. Reasons for this are discussed.

Patients with hypertension in group 1 had values of capillary resistance within the normal range. Those in groups 2 and 3 had significantly lower levels than normal subjects. The possible implications of these results are discussed.

I wish to thank the physicians and surgeons of the United Bristol Hospitals for permission to study their patients, and Miss E. M. Duncan, of the Department of Public Health, Bristol, for help with the statistical analysis.

REFERENCES

- Anderson, G. K., Hawley, E. E., and Stephens, D. J. (1936). *Proc. Soc. exp. Biol. (N.Y.)*, **34**, 778.
 Bell, G. H., Lazarus, S., Munro, H. N., and Scarborough, H. (1942). *Lancet*, **2**, 536.
 Brewer, J. I. (1938). *Amer. J. Obstet. Gynec.*, **36**, 597.
 Brueschke, G. (1955). *Z. ges. inn. Med.*, **10**, 292.
 Coles, D. R., and Gough, K. R. (1960). *Clin. Sci.*, **19**, 587.
 Davis, E. (1946). *Amer. J. med. Sci.*, **212**, 192.
 Fishberg, A. M., and Oppenheimer, B. S. (1930). *Arch. intern. Med.*, **46**, 901.
 Griffith, J. Q., and Lindauer, M. A. (1944). *Amer. Heart J.*, **28**, 758.
 Hecht, A. F. (1907). *Jb. Kinderheilk.*, **65**, 113.
 Holmgren, I. (1957). *Acta med. scand.*, **158**, 269.
 Humble, J. G. (1949). *Blood*, **4**, 69.
 Keech, M. (1958). Personal communication.
 Lack, A., Adolph, W., Ralston, W., Leiby, G., Winsor, T., and Griffith, G. (1949). *Amer. Heart J.*, **38**, 654.
 Lee, R. E., and Holze, E. A. (1951). *J. clin. Invest.*, **30**, 539.
 — and Lee, N. Z. (1947). *Amer. J. Physiol.*, **149**, 465.
 Moore, R. F. (1917). *Quart. J. Med.*, **10**, 29.
 Pickering, G. W. (1955). *High Blood Pressure*. Churchill, London.
 Robson, H. N., and Duthie, J. J. R. (1950). *Brit. med. J.*, **2**, 971.
 Rossman, P. L. (1940). *Ann. intern. Med.*, **14**, 281.
 Scheinker, I. M. (1948). *Amer. J. Path.*, **24**, 211.
 Schweppe, J., Lindberg, H. A., and Barker, M. H. (1948). *Amer. Heart J.*, **35**, 393.
 Soloff, L. A., and Bello, C. T. (1948). *Amer. J. med. Sci.*, **215**, 655.

VITAMIN B₁₂ AND MEGALOBlastic ANAEMIAS IN SOUTH AFRICAN BANTU

BY

J. METZ, M.D.

V. BRANDT, B.Sc.

AND

K. STEVENS, M.B., B.Ch., B.Sc.

*The South African Institute for Medical Research,
Johannesburg*

In the South African Bantu both anaemia and malnutrition are common. Of the forms of anaemia described in this ethnic group, megaloblastic anaemia occurs particularly in association with pregnancy (Adams and Wilmot, 1953; Metz, 1960) and in malnourished infants (Altmann and Murray, 1948; Walt *et al.*, 1956; Shnier and Metz, 1959). Addisonian pernicious anaemia, while less frequent than in white populations, also occurs (Woods and Rymer, 1955; Adams, 1957; Metz *et al.*, 1958).

Although the Bantu diet is often deficient in animal protein, a major dietary source of vitamin B₁₂, there is little published work on levels of serum vitamin B₁₂ in Bantu megaloblastic anaemias. Adams and Forbes (1957) estimated the serum vitamin B₁₂ in 11 Bantu patients with megaloblastic anaemia and in 16 healthy Bantu. Serum vitamin B₁₂ ranged from 481 to 1,701 $\mu\mu\text{g./ml.}$ in the healthy subjects. In five patients with megaloblastic anaemia associated with pregnancy, serum vitamin B₁₂ ranged from 64 to 744 $\mu\mu\text{g./ml.}$, and was below the stated normal range in four of the five patients. In one infant with megaloblastic anaemia the serum vitamin B₁₂ was 94 $\mu\mu\text{g./ml.}$, and in four adults with "nutritional" megaloblastic anaemia the levels ranged from 84 to 309 $\mu\mu\text{g./ml.}$ Serum vitamin B₁₂ was 41 $\mu\mu\text{g./ml.}$ in the one patient with pernicious anaemia. Metz *et al.* (1958) mention the results of serum-vitamin-B₁₂ estimations in six Bantu patients with pernicious anaemia; serum vitamin B₁₂ was 40 $\mu\mu\text{g./ml.}$ or less in all (normal range 100–900 $\mu\mu\text{g./ml.}$).