

THE COAGULABILITY OF VENOUS BLOOD OF NORMAL AND DISEASED LEGS*

A STUDY ON 191 SUBJECTS

B. G. P. SHAFIROFF†, M.D.,
BROOKLYN, N. Y.

H. DOUBILET‡, M.D., I. S. BARCHAM, M.D., and Co TUI, M.D.,
NEW YORK, N. Y.

FROM THE LABORATORY OF EXPERIMENTAL SURGERY, DEPARTMENT OF SURGERY,
NEW YORK UNIVERSITY COLLEGE OF MEDICINE, NEW YORK, N. Y.

THERE has been in recent years a gradually increasing interest in the differences between the blood of diseased and that of normal extremities. Thus, blood drawn from varicose veins associated with complications has been found, on the basis of comparison with values accepted as normal, to exhibit an increase in viscosity and in the concentration of plasma proteins;¹ in carbon dioxide combining power;² and in the rate of sedimentation.³

The clotting time, also, has been studied; and while in the venous blood of thrombo-angiitis obliterans, it was found by Theis⁴ to be shortened in some cases even to less than one minute, in the blood drawn from varicose veins, it was found to be "within normal limits." However, the normal values for viscosity, concentration of plasma proteins, of the carbon dioxide combining power, and of the rate of sedimentation, do not vary within the wide range that the clotting time does, so that a clotting time could vary 300 per cent and still remain "within normal limits." In order, therefore, to determine if there are any actual changes in the clotting time of the local venous blood of an extremity, it would be more reliable to use not the figures accepted as within normal limits, but the clotting time of the blood drawn at the same time from the normal extremity of the same individual. In the following study, this criterion was observed, the venous blood of a normal upper extremity serving as a control.

METHOD.—One hundred ninety-one subjects, comprising four principal groups, were studied. Group I consisted of 28 normal students who had no detectable peripheral vascular disease. The results from this group serve as control for the evaluation of results obtained in the subsequent groups. Group II consisted of 115 patients with varicosities of the lower extremities which were being treated by injections of sodium morrhuate. In this group were many advanced cases, with such complications as varicose ulcers, dermatitis, or peripheral edema of the affected extremity. Determinations of the coagulation time of the blood in the latter individuals, who had been treated with sodium morrhuate, were made only after one to three weeks had passed since the last treatment. In Group III there were 36

* Aided by a grant from the New York Foundation.

† B. G. Shafiroff, M.D., at present Major, M.C., United States Army.

‡ H. Doubilet, M.D., at present Captain, M.C., United States Army.

COAGULABILITY OF VENOUS BLOOD

subjects suffering from conditions comparable to those in Group II, excepting that these patients had never received any treatment. Group IV comprised seven cases of postoperative venous thrombosis and five cases of primary acute thrombophlebitis.

The coagulation time of the blood from the upper and lower extremity was determined in each individual. Blood from the upper extremity was obtained from a cubital vein, that from the lower extremity from the internal saphenous vein at the ankle when there was no varicosity, as in Groups I and IV. In cases in whom there were varicose veins, as in Groups II and III, the blood was drawn from a varicose vein which had not been previously injected.

The determination of the clotting time was carried out according to the technic of Lee and White.⁵ The vein was pierced by a fine hypodermic needle after the application of a tourniquet, and one cubic centimeter of blood was drawn rapidly into a dry syringe. One-half cubic centimeter of blood was placed each in one of two small test tubes and duplicate determinations made simultaneously by two observers. The test tube was tilted at regular intervals until it could be inverted without displacement of the blood mass. This was taken as the critical point for the clotting time. The test was repeated when delay or difficulty was encountered in the process of withdrawing blood from the vein or when any other fault in technic occurred. In 191 subjects, 352 duplicate sets of determinations were made. In none of these was there a difference greater than 20 seconds in the determinations of the two observers, most of the differences being in the neighborhood of ten seconds. The values of the clotting time of the blood from the arm and leg were compared, and the results tabulated in Tables I and II.

TABLE I
ANALYSIS OF INCREASED COAGULABILITY OF BLOOD OF LEG

Group	Total No. of Cases	No. of Cases with Hyper-coagulability	Per Cent of Total	Acceleration in Excess of 59 Seconds		Average Acceleration Time	Maximum Acceleration Time
				No. of Cases	Per Cent of Total		
I.....	28	17	60%	0	0%	30"	59"
II.....	115	83	72%	39	33%	70"	285"
III.....	36	28	77%	13	36%	60"	132"
IV.....	12	11	92%	9	75%	146"	284"

RESULTS.—Referring to Table I, one observes: (1) That there is a slight tendency for venous blood from the lower extremity of normal individuals (Group I) to clot more rapidly than that from the upper extremity: *i.e.*, in 60 per cent of the total number of cases. (2) The blood from varicose veins of individuals in Groups II and III showed an exaggeration of this tendency to faster clotting (72 and 77 per cent, respectively) than the venous blood from the upper extremities of the same individual. (3) In the cases with thrombophlebitis (Group IV) blood from the lower extremity clotted more rapidly than that from the upper extremity in 92 per cent of the cases. (4) Taking those cases of all Groups in which the blood

clotted more rapidly from the lower extremity, the average acceleration in Group I was only 30", whereas in Groups II and III comprising the varicose veins, the average acceleration was 70" and 60", respectively; and in those cases of Group IV with thrombophlebitis the average acceleration was 146". The greatest acceleration in Group I was in one individual, and that was 59". In Group II, the maximum acceleration was 285", while in Group III it was 132". Thirty-three and 36 per cent of the cases with hypercoagulability of varicose vein blood for the two respective groups showed acceleration times in excess of the 59", noted above as the maximum for normal individuals. In Group IV, the maximum acceleration time was 284", while 75 per cent showed acceleration times in excess of 59".

It was previously stated that there was a difference of about 10 to 20 seconds in the determinations by the two observers on any one blood. This may be considered as inherent in the technic. Making allowances in one case for an experimental error of ten seconds and in another case of 20 seconds, the results may be regrouped as in Table I, which may be analyzed as follows:

TABLE II

ANALYSIS OF COMPARATIVE COAGULABILITIES OF VENOUS BLOOD OF UPPER AND LOWER EXTREMITIES-REGROUPED ON BASIS OF OBSERVATIONAL ERROR

(A) 10-Second Observational Error				
	Group I	Group II	Group III	Group IV
Equal.....	5 (18%)	18 (16%)	9 (25%)	0 (0%)
Leg > arm.....	15 (53%)	80 (69%)	24 (64%)	11 (92%)
Arm > leg.....	8 (30%)	17 (15%)	3 (9%)	1 (8%)
(B) 20-Second Observational Error				
Equal.....	13 (46%)	35 (30%)	12 (33%)	0 (0%)
Leg > arm.....	12 (43%)	72 (62%)	23 (64%)	11 (92%)
Arm > leg.....	3 (11%)	8 (8%)	1 (3%)	1 (8%)

For the normal individuals in Group I in the 10-second range of error, only 53 per cent of the cases showed hypercoagulability of lower extremity blood as compared with the upper extremity blood, while the clotting time of the upper extremity blood was faster in 30 per cent of the cases, the remaining 18 per cent being equal. In the 20-second range of error tabulation, blood from the lower extremity clotted more quickly in only 43 per cent of the cases, while upper and lower extremity blood coagulability was equal in 46 per cent of the cases. In no instance did the blood of the lower limb clot more rapidly than the blood of the upper limb by more than 59".

In Groups II and III, however, the results were definitely different. In the ten second range of error tabulation, the blood from the varicose vein was hypercoagulable as compared with the venous blood of the upper extremity in 69 per cent of the total cases in Group II, and 64 per cent of the total cases in Group III. The upper extremity blood was more coagulable in only 15 and 9 per cent of the cases for the two respective groups. When the range of error was set at 20", the same tendency is to be observed. Sixty-two of the cases in Group II, and 64 per cent of those

in Group III, showed a greater clotting tendency of blood from the varicose veins, whereas in only eight and three per cent, respectively, did the venous blood from the upper extremity clot more rapidly. In Group IV, 92 per cent of the total cases showed the blood from the lower extremity to be more coagulable than upper limb blood, whereas the reverse was true in only eight per cent of the cases, these results being the same whether the range of error was as 10" or 20".

In those cases where thrombophlebitis had already become established, there was also an associated marked change in the coagulability of the blood of the diseased extremity as compared with that from a normal extremity of a thrombophlebitis individual. This is plainly visible in the tables. In Groups II and III, it is likewise seen that there is a strong tendency for the same to be true, although not with as great a frequency. This is probably due to the great variation of the degree of disease in the affected vein in both these groups, whereas in cases with established thrombophlebitis, the maximum degree of disease of the affected vessel had taken place. In other words, there are a number of cases in both Groups II and III in which the disease of the affected vessel was so mild as not to interfere with the characteristics of the blood therein. These cases detract from the percentage which might be high enough to present significant differences in the characteristics of blood in a vessel with well-established disease.

There is, thus, a distinct tendency towards acceleration of coagulation in the blood of varicose veins. Where such differences occurred, the magnitude was two times greater than the average difference of the normal individuals, and the maximum difference was five times greater than the maximum difference of the normals. In the cases with established thrombophlebitis, this hypercoagulable tendency of blood of the diseased extremity was so marked, that the average acceleration was four and one-half times greater than in normal subjects, and the maximum five times greater.

COMMENTS.—Some speculations evoked by the above findings may be set down in an attempt to relate this work to its possible clinical use. In regard to the subject of varicose veins, the following questions arise: (1) What change takes place in the blood of a diseased extremity which is reflected in the increased tendency of the local blood to clot more readily than that from the normal extremity of the same individual? (2) Does this rapidity of clotting increase with the functional impairment of the physiology of the veins? (3) Does it disappear in the recumbent position? (4) Do varicose veins showing this hypercoagulable tendency predispose to the development of postoperative thrombo-embolization?

In regard to the marked acceleration of clotting of blood from the veins of extremities with established thrombophlebitis another set of questions may be set down: (1) Is this tendency due to the same change as is to be found in varicose vein blood? (2) Does it antedate the formation of the thrombus?

(3) If so, may it not be developed into a prognostic test which would indicate preventive therapy before actual thrombo-embolization takes place? Each of the answers to these seven questions would constitute the definitive result of seven lines of further investigation.

SUMMARY

1. A study of the coagulation time was made of the blood from the upper and lower extremities of 191 subjects—28 normal, 156 with varicose veins, and seven with established thrombophlebitis.

2. There was found in normal persons, a slight tendency of lower extremity blood to clot faster than upper extremity blood.

3. This tendency was moderately exaggerated, in various degrees, by the presence of varicose veins, and markedly exaggerated in the blood from thrombophlebitic extremities.

4. The possible implications of these findings were discussed.

REFERENCES

- ¹ Heller, R. E.: Pathological Physiology of Varicose Veins. *Surg., Gynec. and Obst.*, **71**, 566, 1940.
- ² DeTakats, G., Quint, H., Tilletsin, B. I., and Crittenden, P. J.: Impairment of Circulation in the Varicose Extremity. *Arch. Surg.*, **18**, 671, 1929.
- ³ Erb, K. H., and Tiefensee, K.: Untersuchungen über das Krampfaderblut. *Beit.z. Klin. Chir.*, **152**, 400, 1931.
- ⁴ Theis, F. V., and Freeland, M. R.: The Blood in Thrombo-angiitis Obliterans. *Arch. Surg.*, **38**, 191, 1939.
- ⁵ Lee, R. I., and White, P. D.: A Clinical Study of the Coagulation Time of the Blood. *Am. J. Med. Sci.*, **145**, 495, 1913.