

A Method for Study of Circulation Time Throughout the Vascular System.*

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Introduction. Most methods utilized in the estimation of circulation time determine the circulation time from the arm where a substance is injected to some point in the head where its arrival is detected. These methods determine the rate of flow in a definite and fixed segment of the vascular tree. A method is desirable for the estimation of the circulation time throughout the vascular system. Spier, Wright and Saylor¹ used a solution consisting essentially of magnesium sulfate and calcium gluconate. The arrival of the solution is indicated by a sensation of warmth appearing first in the throat, then in the hands, perineum and feet. These observers and also Kvale and Allen² noted a prolongation of circulation time to the feet in patients with peripheral vascular disease. A major objection to this method is that the endpoint is entirely subjective.

The intravenous injection of fluorescein followed by the development of a greenish yellow fluorescence in the palpebral conjunctivae and lips when exposed to ultraviolet light has recently been utilized for the study of circulation time.³ This method does not permit observations on the circulation in the extremities as normal skin, unlike mucous membrane, does not become fluorescent. The stratum corneum absorbs most of the ultraviolet rays before they reach the capillaries. In an attempt to modify the skin to favor the development of fluorescence, we applied a wheal to the skin by an intradermal injection

of various substances. It was found that when a wheal was produced by an intradermal injection of histamine, a brilliant fluorescence appeared in the area about the wheal and in the wheal itself, following an injection of fluorescein.

Methods. The material needed is inexpensive and readily available. It consists of the following: a 20% solution of sodium fluorescein, a 1 to 1000 solution of histamine acid phosphate, a 5 cc syringe with a needle attached (preferably 18 gauge), a tuberculin syringe and needle of small caliber, and a portable source of ultraviolet light. In our present studies we are using a solution of histamine in 0.5% novocaine to prevent the pain which often is associated with the application of the wheal. As the source of ultraviolet light, we found that an argon glow lamp which is supplied with a heat resisting purple filter was adequate and simple to apply.[†] With the subject lying quietly in the supine position, a wheal is first raised in the skin by an intradermal injection of histamine acid phosphate. The size of the wheal does not appear to be of importance, but it was usually about ½ cm in diameter. In the present study, the wheal was made in the skin of the middle portion of the leg and in a smaller group of subjects, in the anterior aspect of the forearm. The needle of the 5 cc syringe, containing 2 cc of the sodium fluorescein is then inserted into the antecubital vein. The room is darkened and after about 30 seconds the sodium fluorescein is injected rapidly. The ultraviolet light is directed to one of the eyes of the subject and a stop-watch records the time of the appearance of the fluorescence in the palpebral

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¹ Spier, L. S., Wright, I. S., and Saylor, L., *Am. Heart J.*, 1936, **12**, 511.

² Kvale, W. F., and Allen, E. V., *Am. Heart J.*, 1939, **18**, 519.

³ Fishback, D. B., Guttman, S. A., and Abramson, E. B., *Am. J. Med. Sc.*, 1942, **203**, 535; Lange, K., and Boyd, L. J., *M. Clin. N. Am.*, 1942, **26**, 943.

[†] This consists of a standard 2-watt argon glow lamp enclosed in a small reflecting housing. This unit is readily available and built by the Strob-lite Company of New York.

TABLE I.
Circulation Time in 80 Subjects.

	Time in sec	
	Arm to conjunctiva	Arm to leg
Group 1. Normal individuals (32)	15	20.1
Group 2. Individuals above 50 years of age, no evidence of vascular disease (28)	15.1	24.1
Group 3. Individuals with <i>arteriosclerosis obliterans</i> (20)	15.5	32.9

conjunctiva. The ultraviolet light is then directed to the wheals in the skin and the time of appearance of fluorescence recorded. When several wheals are applied, it is necessary for one observer to inject the fluorescein, while another notes the endpoints at the various sites, recording the time of appearance of fluorescence with the stop-watch.

Results and Discussion. This procedure was carried out in 80 subjects. They were divided into 3 groups. Group 1 includes 32 individuals, all below the age of 50 and free from any evidence of peripheral vascular disease. Group 2 consists of 28 subjects above the age of 50, but with no definite signs of disease of the peripheral vessels. Group 3 includes 20 patients who had definite evidence of vascular disease in the lower extremities. The type of vascular involvement in each instance could be classified as *arteriosclerosis obliterans*. In each of the 80 subjects, the circulation time was recorded from the arm to the conjunctiva and from the arm to a wheal in the leg (arm to leg time). The results are summarized in Table I. In 20 instances, coincident circulation times were recorded from the arm to the conjunctiva and from the arm to a wheal in the opposite arm (arm to arm time). By subtracting the "arm to conjunctiva" time from "arm to leg" and "arm to arm" times, one may obtain a reasonable approximation of the rate of flow in the arterial segment to the leg and arm. It will be noted from Table I that the average circulation time from "conjunctiva to leg" in normals is 5.1 seconds, in the group of elderly subjects 9 seconds, and in the *arteriosclerosis obliterans* group 17.4 seconds. Spier and his associates¹ found the average time from "throat to foot" in normals to be about 14 seconds, while

Kvale and Allen² report this interval to average about 20 seconds. While our results show the "conjunctiva to arm" time in normals to vary from 1 to 3 seconds, the average reported by Kvale and Allen for "throat to hand" time is from 9 to 10 seconds. The exact explanation for the differences in results is not clear. It should be stated as a possible explanation that any method in which a sensory reaction is used as the end point may include a latent period during which the perception of the sensation develops. It is quite possible that, due to a lower reactivity of the sensory endings in the extremities, a higher concentration of the magnesium-calcium solution must develop at the site of stimulation in order to call forth a response. Thus the time interval observed by this method between the response in the throat and the reaction in the extremities may include not only the circulation time between these points, but also the time required for the development of the sensory response at the end point.

As compared with the calcium-magnesium method, the present procedure shows a sharper differentiation between normal individuals and those with peripheral vascular disease. As compared with a "conjunctiva to leg" time of 5.1 seconds in normals and 17.4 seconds in *arteriosclerosis obliterans* by our method, Kvale and Allen² report an average "throat to foot" time of 20.3 seconds in normals and 26 seconds in *arteriosclerosis obliterans*.

Summary. An objective method is described for the study of circulation time throughout the vascular system. The results of the application of this method in normal subjects and in individuals with peripheral vascular disease is reported.