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STUDIES ON THE VELOCITY OF BLOOD FLOW

I. The Method Utilized[1]

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An adequate flow of blood to the tissues implies two things. In the first place an adequate amount of blood must be expelled from the heart per unit of time. In the second place this blood must be transported to the site of utilization at an adequate speed. The former aspect of the circulation, the minute volume output, has received considerable study. The second aspect, the velocity of blood flow, has not. Nevertheless, discussions of the probable velocity and its significance in maintaining the physiological integrity of the body have frequently been reported.

HISTORICAL RÉSUMÉ OF METHODS EMPLOYED IN STUDYING THE VELOCITY OF BLOOD FLOW

With the discovery by Harvey in 1628 (1) of the movement of blood in a circuit, the problem of the velocity at which the blood flows first presented itself. Not until 1733, however, when Stephen Hales (2) published his penetrating inquiries was the question of the velocity of blood flow discussed in quantitative terms. His grasp of the essentials of the problem was extraordinary. From his estimation of the capacity of the left ventricle, the diameter of the base of the aorta, and the pulse rate he computed the velocity of blood flow in the aorta of the horse.

The problem of the velocity of blood flow received its next impetus in 1827, when Eduard Hering (3) measured the velocity of blood flow by injecting a solution of potassium ferrocyanide at one point and

[1] This study was aided by a grant from the Proctor Fund of the Harvard Medical School for the Study of Chronic Disease.

determining its time of arrival in the blood at another point in the vascular circuit by testing the samples of withdrawn blood for prussian blue. He measured in this way the circulation time from the right to the left external jugular vein.

In 1850, Volkman (4) constructed the haemodromometer, a pendulum device which gauged the velocity of blood flow by recording the movement of a pendulum placed in the lumen of a blood vessel. The inertia of the instrument was sufficient to distort the results. But aside from this defect the obstruction imposed by the instrument to the onward flow of blood must have altered the velocity.

The haemotachometer designed by Vierordt (5) was a distinct improvement. His method resembled Hering's, but whereas Hering's observations were confined solely to horses, Vierordt extended his to rabbits, hedgehogs, squirrels, cats, dogs, ducks, cocks and geese. Actually, he observed the time necessary for the fastest particle of blood to traverse various paths. From these data he attempted to estimate the mean velocity (page 119). Vierordt improved Hering's method by affixing a number of cups to a disc (page 56), which was rotated at a uniform and known rate. In each of the cups he collected samples of blood drawn at intervals of one second.

In the latter part of the nineteenth century, there were repeated attempts to estimate the velocity of the blood in the arteries and veins by means of Cybulski's photohaemotachometer and O. Frank's differential manometer. The insertion of such devices into the blood stream demanded much manipulation and introduced so many extraneous physical factors that the results were difficult of accurate interpretation, and therefore failed to clarify the problem.

More fruitful was the approach of G. N. Stewart (6) who studied the circulation time by injecting a hypertonic solution of sodium chloride into one jugular vein, and by ascertaining its time of arrival in another vessel. The time of arrival was signalled by a change in the electrical conductivity of the blood in the vessel, which was placed between two non-polarizable electrodes. He also utilized methylene blue injections observing by transillumination the time at which the dye appeared in the common carotid artery. He studied the circulation times of many pathways in various animals and also studied the circulation times of individual organs.

In 1922, E. Koch (7) presented his measurements of the circulation time in man in both normal and pathological states. His method consisted of the injection of 1.0 cc. of a 1.6 per cent solution of fluorescein into the cubital vein of one arm and then obtaining samples of blood at five second intervals from the cubital vein of the other arm. The dye, therefore, traversed the veins to the right ventricle, the lung circulation to the left ventricle, the aorta, the arteries of the arm, the peripheral capillaries of the arm, and then finally, the vein from which the blood was collected. His results will be discussed later. It should be noted, however, that withdrawal of blood is feasible only from the cubital vein. In order to determine the time of arrival of such a dyestuff, it is necessary that a constant stream of blood flow from the arm through the needle to the collecting tubes. The formation of clots, the inaccessibility of veins, alteration of flow by the introduction of the needle into the vein, all necessarily interfere with the trustworthiness of such a method.

Because of the inaccuracies and limitations of previous methods, we felt the necessity of developing a more satisfactory approach to this fundamental problem.

Theoretically the most desirable measurement of the velocity of blood flow consists in establishing the separate velocities of each minute portion of the blood along the many separate paths. When one considers that the innumerable vessels in the body are constantly changing in size and elasticity and that the blood is a suspension of corpuscles in a fluid medium, the impossibility of fulfilling the ideal requirements becomes obvious. The problem is further complicated; any mean velocity measurements which depend on the insertion of a mechanical device into the blood stream defeats its ends and can therefore, not be considered for clinical application. The most feasible method appears to be the injection of some substance at one point in the body, and the measurement of the time of its arrival at another point. Consideration of the problem shows that the substance to be used must fulfill the following requirements.

1. The substance must not be toxic in the amounts utilized. Toxicity is of course a relative quality, for any substance, if given in sufficiently large amounts, may bring about grave consequences.

2. The substance should not be present previously in the body.

Estimation of additional amounts of substances already within the body is always subject to error. Weber's law, moreover, is applicable. According to this law, the increase of stimulus necessary to produce an appreciable increase in sensation must always bear the same ratio to the whole stimulus. If, accordingly, a substance were already present, greater amounts of that substance must be injected to produce appreciable changes at the point of detection.

3. The substance must not in any way disturb the very phenomena under investigation. Toxicity would introduce such an error. The introduction of hypertonic salt solution would also cause an error for it would alter the blood volume, vary the speed of blood flow, and thereby modify the very phenomenon under investigation.

4. It is desirable that the substance disappear from the body with sufficient rapidity to allow of repeated measurements.

5. The substance must be readily detectable in minute amounts. Were this impossible, varying dilutions of the substance would be all the more likely to produce correspondingly variable results.

Initial attempts were made in animals to test the usefulness of various substances. We injected intravenously salts such as those of lithium and strontium, and examined spectroscopically drops of blood from various parts of the body. The results were unsatisfactory.

The use of the active deposit of radium (or radium C) had yielded a method which fulfills the foregoing criteria and has proved entirely satisfactory.[2]

The method consists of the injection of the active deposit of radium at one point in the body, and the detection of its time of arrival at another point. The active deposit is particularly suited to the purpose because of the following properties. In the first place, it is nontoxic in the amounts necessary for the purpose. Quick and Duffy (8) at the Memorial Hospital in New York in studying the possible therapeutic effects of radium C in patients with advanced generalized carcinomatosis gave repeatedly intravenous injections of 50, and 75 millicuries without any consequent ill effects. They studied the urine for signs of renal irritation, and the blood for evidence of nitrogen retention, without noting any untoward effects. No significant

[2] In a forthcoming paper, we intend to describe the method of preparation of radium C.

changes were noted in the red blood cell count or hemoglobin. Our own experiments on animals and, as will appear below, our subsequent study of the effect of radium C in ourselves and in patients has uniformly showed an absence of any objective or subjective ill effects. In a few patients with generalized carcinomatosis large amounts of radium C were administered; the amount necessary, however, for a measurement is only one to four millicuries.

Active deposit fulfills the other requirements previously mentioned. It is not present normally in the body. The injection of radium C into animals and later into human beings has shown a uniform absence

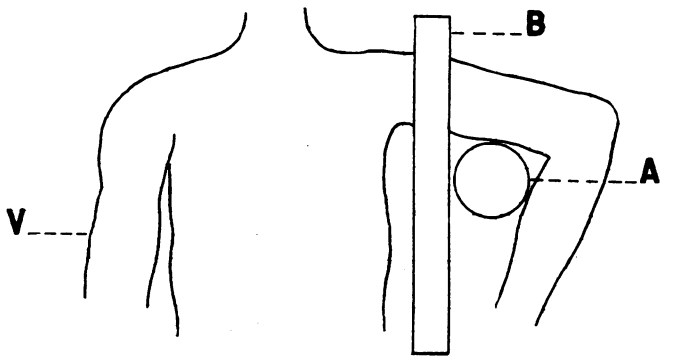

FIG. 1. DIAGRAM OF RELATION OF THE LEAD SHIELD AND THE DETECTING DEVICE TO THE PATIENT

A, detecting device; *B*, lead shield through which the left arm passes; *V*, right arm.

of any discernible alterations in the blood pressure or the ventricular rate or the ventricular rhythm. The properties of the active deposit of radium are such, moreover, that observations can be repeated after approximately three hours, inasmuch as the active deposit decomposes to within 3 per cent of its initial value at the end of that time. As to its detectability in small amounts, the active deposit leaves nothing to be desired since the presence of a single atom can be detected.

The active deposit lends itself particularly to the purpose of measuring the velocity of blood flow because of its radiation; for, being a member of the radium family, it gives out penetrating radiation in

the form of beta particles or electrons, and gamma rays which are comparable to hard x-rays. These radiations penetrate ordinary materials such as tissues and air, but can be stopped by lead. If the active deposit of radium is injected into the vein of one arm (fig. 1), it gives off radiation as it is carried up the arm to the right side of the heart and thence through the lungs to the left side of the heart. The lead shield *B*, prevents the radiation from reaching the detecting device *A*. As soon as the radium active deposit reaches the arterial vessels of the arm beyond the lead block, the radiations are no longer separated from the detector *A*, by lead. Instead, they penetrate the tissues, traverse the air, and enter the detecting device, where they appear as definite white streaks.

DESCRIPTION OF THE APPARATUS

1. The detecting device

To secure a suitable detecting device proved to be a formidable undertaking. The usefulness of instruments for detecting minute amounts of radioactive substances depends on their ability to detect the characteristic beta and gamma radiations which are emitted from within the atom. These radiations cause ionization of any gas they traverse. Conversely, under suitable conditions, the onset of ionization in a gas can therefore be assumed to indicate the presence of the radiation of a member of a radioactive series.

The use of an electroscope as a detector was attended with great difficulties. Perfectly satisfactory shielding of the electroscope from the radiations of the active deposit as it coursed through the body was impracticable. Morever, the precise instant at which the radium active deposit arrived was extraordinarly difficult to ascertain by this device.

Kovarik's modification of the Geiger counting chamber was likewise tested (9). The necessity of a source of constant high potential, the instability of the steel needle electrode, and the relatively high number of spontaneous discharges discouraged the choice of this mode of detection.

We also attempted to use parallel plate ionization chambers. We found, however, that the large electrical capacity of the plates reduced

the sensitivity of the ionization chambers, even when we used low pressures and introduced various vapors to obtain the greatest possible amount of ionization by collision.

The use of a cloud chamber of the C. T. R. Wilson type (10) approached more closely our requirements. In principle this apparatus consists of an air-tight chamber saturated with water vapor. At the bottom of the chamber is a piston which falls periodically, and in so doing produces an adiabatic expansion of the enclosed volume of air and water vapor. The vapor is cooled to such an extent by this expansion that it becomes critically supersaturated. In this state, the vapor condenses in the form of minute droplets upon any small particles such as dust, which are suspended in the gas. If no dust particles are present, the water vapor condenses in minute droplets upon any electrically charged bodies such as ionized molecules. If, for instance, a gamma ray or beta particle should traverse the chamber and create an ionized path, while the chamber is in the condition of critical supersaturation, the water vapor would condense as minute droplets along the ionized path. With proper illumination, this ionized path appears as a white streak. Unfortunately, a constant state of supersaturation can not be maintained, but by the use of a reciprocating piston device of the Shimizu type (11), the chamber can be rendered periodically susceptible to the formation of droplets along any ionized path. The critical degree of supersaturation, therefore, is attained on each descent of the piston.

The detecting device which we finally adapted from that of C. T. R. Wilson may be represented diagramatically (fig. 2). Letter *F* is a brass cylinder into which a duralumin piston, *D*, is accurately fitted. This piston is connected below to a shaft, *R*, which is moved up and down by a cam, *P*. Every revolution of the cam *P* causes the piston, *D*, to drop suddenly from a high to a low position. The top and the bottom positions and therefore the extent of the fall are all adjustable by the bearing *S*. This device is of considerable importance, for the degree of vapor supersaturation required is a critical one. It is dependent on variable conditions such as room temperature and the amount of water vapor initially present in the chamber. Once the adjustments are made, however, by means of varying *S*, no further manipulations are necessary during the time of an experiment.

Upon the top of a cylinder is screwed the chamber consisting of a threaded brass collar, *B*, celluloid ring, *C*, and glass top plate *A*. The celluloid ring consists of a strip of celluloid 0.005 inch in thickness, the ends of which are stuck together with amyl acetate. By means of rosin it is rigidly set into a groove in the brass collar below, and into a corresponding groove in the glass plate above. The rosin must

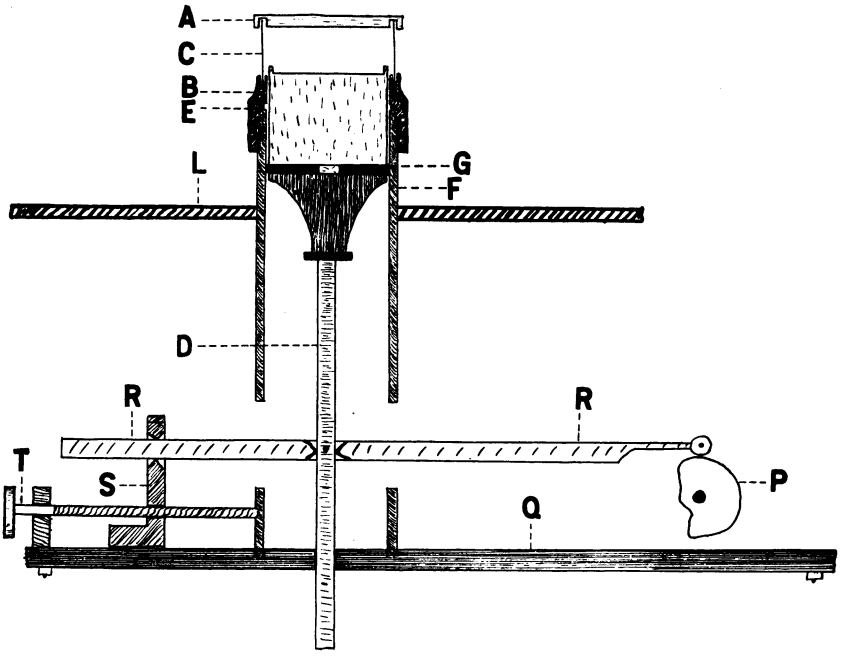

FIG. 2. DIAGRAM OF DETECTING DEVICE

A, glass top plate; *B*, threaded brass collar; *C*, celluloid ring; *D*, duralumin piston; *E*, rubber washer; *F*, brass cylinder; *G*, leather washer; *P*, cam; *Q*, steel bottom plate; *R*, duralumin shaft; *S*, support and bearing for shaft; *T*, adjusting screw; *L*, shelf for arm rest.

be heated to a temperature of 110° to 130°C. and it must be free of air bubbles.

The top of the piston and the bottom of the cover glass are coated with gelatin. The gelatin covering the piston is blackened with India ink. The gelatin covering the top glass plate contains a small amount of copper sulphate and can therefore, be used to establish an electri-

cally negative charge. The charge passes into the chamber by means of a tongue of lead foil, leading to a thin ring imbedded in the copper sulphate gelatin. The charge established on the top plate consists of about minus fifty volts. It serves to dispel the tracks formed at each descent of the piston. In this way the chamber is cleared for the new tracks of the next expansion. The piston is at ground potential. The charge on the top plate is applied during only a portion of the upstroke. During the rest of the time the top plate is grounded. The regulation of the charge on the top plate is accomplished by means of an adjustable commutator operated from another cam, not shown in the diagram but concentric with the cam, *P*.

The cycle of events is therefore as follows. During the downstroke of the piston the gas in the chamber is suddenly expanded and becomes supersaturated for an instant. If, during this instant, any primary or secondary beta particles are travelling through the chamber, the water vapor condenses along that path and when properly illuminated appears as thin, white streaks. The streaks or tracks settle slowly under gravity, but before they have moved far the piston returns to its former high position and the gas is again at its initial volume. Part of the drops immediately evaporate. The others are swept to the top of the piston below by the repelling force of the negative electric charge on the top plate. The chamber is again clear and ready for another expansion.

The instrument may be operated at any rate up to three or five expansions per second, but about one per second has proven most satisfactory. The moving parts are placed below the cylinder head so that the patient's arm may be conveniently laid upon the iron plate, *L*, and brought against the thin celluloid rim *C*.

In the actual observations we have placed the detecting device within the bend of the elbow, so that the ionization chamber is exposed to the radiation from the brachial artery and its branches. The arm of the patient passes through a lead block 8 cm. in thickness, which serves to prevent radiations from the rest of the body from reaching the detector.

PROCEDURE OF THE MEASUREMENTS

Sodium chloride is exposed to radium emanation for an appropriate length of time, during which radium C is deposited upon the salt.

The method utilized is that described by Theis and Bagg (12). The sodium chloride is then dissolved in sterile distilled water and its radioactivity measured by means of a gamma ray electroscope. The volume of the solution, which is contained in the syringe is usually about 0.5 cc.

The measurement of the velocity of blood flow is made under basal metabolic conditions, no food being taken by the patient after supper on the preceding evening. The patient lies down in bed and rests for at least twenty minutes. The left arm is passed through the lead block and arranged around the cylinder of the cloud chamber. The active deposit is not injected for at least twenty minutes after it has been removed from exposure to the emanation to allow the alpha ray activity to decay to four per cent of its initial activity (13). The cubital vein of the right arm is entered with a sharp needle to which is attached a three-way stopcock. A small amount of blood is withdrawn in order to be certain that the needle lies free within the vein. The stopcock is then turned so that the needle communicates with a manometer filled with a solution of sodium citrate. The level of the top of the sodium citrate in the manometer is then compared with the level of the right auricle. The details of the measurement of venous pressure are practically those published originally by Moritz and Tabora (14).

The syringe into which the blood was drawn is replaced by one containing the radium active deposit. The stopcock is then turned and the 0.5 cc. solution containing a minute volume of active deposit is quickly injected into the vein. The injection time is always less than one second. As the active deposit courses through the body an occasional track is visible within the cloud chamber. With the arrival of active deposit within the arterial vessels of the arm, beta particles and gamma rays pass through the tissues of the arm, traverse the thin celluloid rim, enter the cloud chamber, and there become visible. Instead of an occasional track, at least two or more tracks are visible at succesive expansions. The time of arrival of the active deposit in the arterial vessels of the left arm is registered by means of a stop watch. The difference between the time of injection and the time of arrival gives the velocity of blood flow between the two points. The amount of active deposit utilized for a determination has been from

1 to 6 millicuries. On theoretical grounds it is difficult to conceive of such amounts causing any toxic effects. In practice we have verified the theoretical expectation.

RESULTS

The primary purpose of the preliminary measurements was rather to test the method than to gain additional knowledge of the circulation. The velocity of blood flow (measurement numbers 1, 2, 3, 4, 5, 6)

TABLE 1

Number	Date	Diagnosis	Millicuries injected	Circulation time
2	February 28, 1925	Carcinoma of esophagus	52	18
5	March 2, 1925	Metastatic carcinoma of liver	17	20
10	March 2, 1925	Chronic myocarditis	18	32
3	March 3, 1925	Carcinoma of stomach	33	18
9	March 3, 1925	Jaundice, bradycardia	5	30
8	August 22, 1925	Emphysema	35	28
7	August 22, 1925	Emphysema	5	25
13	August 28, 1925	Auricular fibrillation	38	55
12	September 1, 1925	Auricular fibrillation	4	53
1	August 28, 1925	Chronic arthritis	2	15
4	August 29, 1925	Normal	2	18
6	September 1, 1925	Normal	1	21
14	August 29, 1925	Cardiac decompensation	4	65
15	September 1, 1925	Chronic myocarditis Cardiac decompensation	2	71
11	September 1, 1925	Auricular fibrillation Cardiac decompensation	7	50

(table 1) was studied in patients in whom the cardio-respiratory system was normal. The time required for the substance to flow from one arm to the other arm was found to be from fifteen to twenty-one seconds. These results are in contrast with the velocities recorded in three patients who showed signs or symptoms of cardiac decompensation. In these patients (numbers 12, 14 and 11), the times noted 53, 65 and 50 seconds clearly belong to a different order.

Observations were repeated in the same individuals to test the reliability of the method. Measurements 7 and 8, 4 and 6, 12 and 13 all show agreement within three seconds. Of particular interest are

numbers 7 and 8, for the amount of deposit utilized in the first is sevenfold that injected for the second measurement.

In all these patients the urine was carefully examined immediately before and immediately after injection, and uniformly failed to show any signs of renal irritation. No anemia followed the injection of radium C in the amounts used.

CONCLUSIONS

A new method is presented for the measurement of the velocity of blood flow in man. The active deposit of radium is injected into the antecubital vein of one arm and its time of arrival in the other arm is detected by means of a modified C. T. R. Wilson cloud chamber device. The advantages of the method are as follows:

1. The volume of fluid injected is very small.
2. The substance injected is non-toxic in the amounts utilized.
3. The presence of extraordinarily minute amounts of the substance can be detected with certainty.
4. The radiations by traversing the tissues of the arm automatically indicate the time of arrival of the active deposit.
5. No withdrawal of blood is necessary.
6. The method is objective requiring no coöperation on the part of the patient.
7. The method gives a quantitative estimate of a fundamental aspect of the circulation.

We wish to express our appreciation to Dr. Francis W. Peabody for his constant advice and encouragement.

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