

STUDIES ON THE CIRCULATION

IV. FURTHER ANALYSIS OF THE INJECTION METHOD, AND OF CHANGES IN HEMODYNAMICS UNDER PHYSIOLOGICAL AND PATHOLOGICAL CONDITIONS

W. F. HAMILTON, JOHN WALKER MOORE, J. M. KINSMAN AND
R. G. SPURLING

*From the Department of Physiology and Pharmacology, the Department of Medicine,
and the Department of Surgery, University of Louisville School of Medicine,
Kentucky*

Received for publication July 6, 1931

As the injection method has developed (1, 2, 3, 4, 7), several questions have arisen in our minds, as well as in the minds of those who have constructively criticised it (15). These questions involve consideration of the mathematical basis of the time-concentration curve of consecutive arterial samples, when a dye is injected into a vein; the calculation of the volume of blood in the thorax; and the effect upon the curve of such factors as different rates of flow in parallel streams (as might occur in the lungs), of mixing of dye in the heart and great vessels, and of diffusibility of various dyes.

The purpose of this paper is to describe in detail the present technique of the procedure; to present new evidence in answer to the above questions, and to illustrate the application of the method with data gathered from experiments on man and animals.

Technical details of experimental procedures and calculations. In the experiments on animals and with artificial systems, the technique is the same as that already described (1, 2, 3, 4). In the experiments on man, the puncture technique has been modified. We have attempted (1, 3, 4), with varying success, punctures of the radial, brachial and femoral arteries. The one most easily punctured is the femoral but has necessitated an awkward and uncomfortable posture on the part of the subject. This difficulty has been eliminated by having the subject near the edge of the bed with a semicircular piece (to receive the sampling kymograph) about a foot in radius removed from the center of the edge of the mattress and of a wooden platform under the mattress and on the bed. He is supported with pillows in a comfortable position which is halfway between the supine and lateral-recumbent posture. A needle, which has been found satisfactory for sampling from the femoral artery, is made from 19 G. stainless steel needle tubing. Two centimeters from the sharpened end is a 45° bend. One centimeter behind this, a collar is sweated on to facilitate handling. Three or 4 cm. behind this and at the other end of the needle is a 90° bend in the same direction as the 45° bend. A needle of this shape cannot be cleaned with a stylet;

flushing with two per cent alkali, however, keeps it clear. If the puncture sites are properly novocainized and the work carried out calmly and surely, the samples can all be taken very quickly, with little excitement or anxiety on the part of the subject, as evidenced by lack of increase in heart rate.

The concentration of the dye in the samples is determined colorimetrically in a micro-colorimeter (B and L) against a standard made up to known strength.

The dilutions are made in essentially the same fashion as before described (1), except that with brilliant vital red which we are now using,¹ 0.01 per cent NaOH solution is substituted for the 1 per cent NaOH which was used with phenoltetraiodophthalein.

It occasionally happens that when the two standards are read in the colorimeter against each other, the weaker standard gives a higher reading than it should. This is because of adventitious color which can be recognized in the undyed serum, as serum pigment or dye left over from a previous experiment. This adventitious color cannot be read against the blood standard because the latter is sophisticated by the same color. It is the same in both standards but bears in each a different relation to the added dye. Its amount can, therefore, be calculated by

$$\frac{x + 125}{x + 250} = \frac{R \ 250}{R \ 125} \quad \text{I}$$

where x is the unknown adventitious color, 125 and 250 are the concentrations in milligrams per l. of dye added to the blood for the weak and strong standards respectively, and $R \ 125$ and $R \ 250$ are the actual readings at which the weak and strong standards match. Thus, if the readings are $R \ 250 = 4$ and $R \ 125 = 7.1$ the adventitious color would come out as equal to a dye solution whose concentration is 25 mgm. per l. in blood. The standards would then be considered as containing 150 and 275 mgm. per l. For convenience in calculation the standards are set at the reciprocals of these figures, viz., 6.67 mm. and 3.33 mm. or a multiple, and the samples read as indicated in the previous section. The figure representing the adventitious color would, of course, have to be subtracted from the value attached to each sample.

In practice one usually finds that the two standards give a good match at depths which correspond to their supposed concentrations. The equation then would work out $x = 0$ and no allowance would have to be made for adventitious color. An occasional sample, however, shows a color which is of a different hue in the colorimeter, and whose best match gives a reading that diverges widely from that of the rest of the series. Such a sample has been exposed to some accident that has caused hemolysis and should be disregarded.

After the readings are made, and corrected if necessary, they are plotted as ordinates on semi-logarithmic paper (Keuffel & Esser Co., N. Y., no. 358-70) against time in seconds as determined by measuring from the middle of the injection mark to the middle of each tube. A smooth curve is then drawn through the points on the upstroke and peak of the curve. The points on the downstroke will, if the work has been properly done, indicate a straight line. This line is then drawn through these points and prolonged through one cycle of the paper (e.g., from ordinate 100 to ordinate 10).

After the curve is drawn as described above, the next step is to read and add together (S_1) the height, in milligrams per liter, of the intersection of every second-ordinate on the curve, from its beginning to where, on the downstroke, it enters the

¹ Congo Red, Niagara Sky Blue 6 B, and Special Blue T. S. S. (National Aniline Co.) were all used and found to be less satisfactory than the Brilliant Vital Red.

straight line. The ordinate values of the points at second intervals on the straight line as it crosses the first cycle on its downward course are summated separately (S_2). As this line crosses the next cycle (10 to 1) with unchanging slope, the summed points (S_3) will be, very closely, one-tenth of the summed points in the cycle above (S_2). The next cycle will contribute (S_4) one-hundredth of the value of S_2 and so on. The sum (S) of all the values, in mgm./l. read at each second's intersection of the curve, when the curve is prolonged to infinity would be $S_1 + S_2 + S_3 + S_4$, etc. How far it is necessary for practical purposes to prolong the series depends upon its slope; the larger S_2, S_3, S_4 , etc., are, the more nearly horizontal the curve. One's judgement, and the accuracy required of the calculation, should easily determine the end point.

For convenience in calculating, the formula (2, 3)

$$F = \frac{60 i}{c t} \quad \text{II}$$

has been simplified to

$$F = \frac{60 i}{s} \quad \text{III}$$

where F is the flow in liters per minute, c is the average concentration in mgm./l. during the primary curve, and t is the duration in seconds of the curve used in the calculation. Since $ct = \frac{s}{t}$ the arithmetic is simpler with the second equation.

VOLUME-FLOW-CONCENTRATION RELATIONSHIPS IN SIMPLE SYSTEMS. When dye is injected into the vein of an experimental animal and consecutive samples taken from some point in the arterial system, it is seen that the curve of concentration rises to a maximum, rounds off, and descends a little more slowly than it ascended; and that there is unmistakable evidence (2, 3) that the logarithm of the concentration finally assumes a linear relationship with time. The relationship found in the descending limb of the curve is expressed by the compound interest law (2) (for details of which any text on calculus can be consulted). The formula is as follows:

$$C_t = C_o e^{-\frac{f}{XV} t} \quad \text{IV}$$

Where C_o is the original concentration in milligram per liter.

C_t is the concentration after the elapse of t seconds.

e is the mathematical constant 2.718+.

f is the flow in liters per second.

V is the volume of the system in liters.

X is a factor to correct for the fact that mixing is not instantaneous.

This equation cannot be employed in calculating quantitative data on account of the difficulty of assigning a definite value to X . It is introduced here for the purpose of emphasizing the fact that blood flows through the lungs in a manner that is essentially predictable, and washes

out the injected substance in such a fashion that the time-concentration relations conform to a mathematical formula. X can be determined by substituting for V in equation IV, its value as obtained by multiplying the mean circulation time by the flow (*vide infra*), and would be an index as to how large a part of the volume between the needles the dye was simultaneously mixed with. The physiological significance of this factor is at present undetermined.

Although from the evidence published above and that cited elsewhere it seems clear that one may calculate the flow from the time-concentration relationships, it has not been demonstrated conclusively that the volume of the system carrying the flow can be calculated with equal assurance. Indications of the nature of this demonstration have already been published (2).

It was assumed by Stewart (5) and the assumption accepted by Blumgart and Weiss (6), that the fastest circulation time does not differ materially from the mean circulation time. This idea rests upon the argument that in flowing through a complicated capillary pathway a particle of blood is passed in and out of the axial stream so many times that its average velocity would in the end be no different from that of all other particles in the same stream. The argument neglects the obvious fact that some pathways are longer and more tortuous than others, and hence take more time in passage. A casual glance at the curves given in this and earlier papers, particularly the heart-lung perfusion curves, leads inevitably to the conclusion that the shortest circulation time is *not* of the same order as the mean or average circulation time.

We at first thought it possible to determine the average time by finding the ordinate which divided the area of the curve into two equal parts (2). If the curve is symmetrical this procedure is adequate, and most of the curves with which we first checked the volume calculation were nearly symmetrical, and the calculations checked. They failed to check in curves from the more complicated systems. These curves were markedly asymmetrical and so were those from the cases of decompensated heart disease.

The average time M it takes the dye to go through a system can be calculated from the time-concentration curve by the following formula:

$$M = \frac{T_1C_1 + T_2C_2 + \dots + T_nC_n}{C_1 + C_2 + \dots + C_n} \quad V$$

Let the concentration readings be C_1, C_2, \dots, C_n at times T_1, T_2, \dots, T_n . M is the T -coördinate of the center of gravity of the curve. The curve may also be replotted on linear coördinates and cut out. The T -coördinate upon which the piece of paper (of uniform thickness) thus formed balances on a knife edge is approximately the T -coördinate of the

center of gravity of the curve, and the time from the middle of the injection period to this time, when multiplied by the flow, gives the volume of the system within the limits of experimental error.

The mean circulation time has its importance from the obvious fact (5, 6), that during this time the flow will have displaced a volume equal to that within the system, and hence that

$$V = M f \quad \text{VI}$$

where V = the volume contained in the system, M , the average time it takes the injected substance to pass through the system, and f the flow per second. Using this formula we find that V is correct within the limits of colorimetry in all sorts of artificial models in some of which the dye solutions flow through empty bulbs, in some through bead-filled bulbs and in some through combinations of these in series or in parallel.

VOLUME-FLOW-CONCENTRATION RELATIONSHIPS IN COMPLEX SYSTEMS. If the flow through each of two capillary beds is the same in proportion to their volume the curves of dye concentration in successive samples

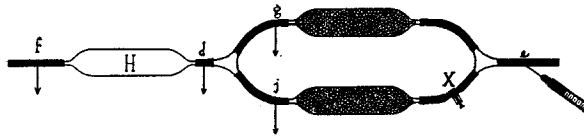


Fig. 1. Apparatus through which dye is carried by a stream of water. Bulbs in parallel are filled with beads.

taken at the exit of each system are of course identical. See figure 1. The mixture of the two identical streams would have the same time-concentration relationships as either one. Experiments have shown that it is possible to calculate both flow and volume within the limits of experimental error in set-ups of this type.

If, on the other hand, the flow through the two parallel capillary beds is not in the same proportion to their volume, the time-concentration curves assume bizarre shapes, simulating roughly curves in which recirculation has occurred. Figure 2 has been constructed in such a way that in case of b_3 the flow through one bulb is twice that in the other bulb of the same size (see fig. 1); in case of b_4 it is three times, in b_5 , four times and b_6 , five times.

The flows and volumes as calculated from the curves using equations III, V and VI, have been found to agree within one or two per cent with the flows determined on the basis of the experiments used in constructing the curves.

Now, if we attempt to get at these quantities (V and F) by prolonging the straight line in the earlier part of the curve—a procedure which is necessitated by the situation in animal experiments—we get the figures given in table 1.

From this it would seem that when an error appears which is due to failure of the two branches of the stream to flow at the same rate in proportion to their volume, there is a limit to the degree to which the flow figures may be affected. The above possibilities which we have tested graphically involve the assumption that the two beds with unequal flow have equal capacity. If, however, the slower bed have the smaller capacity, the error would *ipso facto* be proportionately reduced. If, on the other hand, the slower bed have the larger capacity, an incongruity might arise in that the smaller and faster bed would predominate in the volume calculation and give a result which might warn one that something was awry.

It must not be thought that in the animal body the possibilities which we have analyzed in detail are permitted by the situation to bring about errors of as large magnitude as those which have come out in these illustrations. When dye is injected into a vein it first mixes in the great veins and right heart with a volume of blood (part of V), is then separated

TABLE 1
Comparison of flows and volumes with those calculated from "prolongation" of the curves in figure 2

CURVE	CALCULATED F <i>cc./min.</i>	CALCULATED		
		Error <i>per cent</i>	V <i>cc.</i>	Error <i>per cent</i>
A	1,080	0	112.5	+4.6
b ₂	1,860	12.4	228.0	+6.0
b ₄	1,844	21.7	197.0	-8.4
b ₅	1,670	18.2	175.0	-18.6
b ₆	1,543	16.2	157.0	-27.0

into many parallel paths and finally combines and is mixed further and with more blood in the left heart and arteries, before it is sampled for the concentration curve.

In order to inquire into the significance of these factors, an experiment was performed in which the flow through a set-up such as figure 1 was sampled for a time-concentration curve. The flow was much faster through one bulb than through the other. When the samples were taken at d curve $A B D^2$ results.

² The irregularity (notch) at the beginning of the curve in figure 3 is accidental. The syringe stuck when the dye injection was partly in. The injection was thus made in two parts giving a curve of greater irregularity than was to have been expected from considerations which have appeared above. Other curves more nearly like those in figure 2 could have been substituted for figure 3, but it was thought better to illustrate the influence of common mixing such as would occur in the heart and great vessels, upon this very bizarre curve. The fact that this curve is changed to one that is of the type that is usable physiologically gives a favorable answer to a rather severe test.

If, however, the stream is allowed to pass through a common mixing chamber *H*, figure 1, and the samples taken at *f*, figure 1, the curve changes to *A'B'C'*. These two curves were taken in two rows of sampling tubes on the same kymograph, with one injection of dye. The flow and volume calculations were as shown in table 2.

Since curve *ABD*, figure 3, would be hidden by recirculation in a physiological experiment, and hence would not be available, comparison must be made between the figures in the last two columns. Obviously the mixing in the common parts of the path has done much to eliminate the irregularities in the curve and to facilitate the calculations of both flow and volume.

In animal experiments this factor is important. Dye in passing through common parts of the path (the heart, great veins and arteries) would mix with the blood in such a fashion as to straighten out irregularities in the

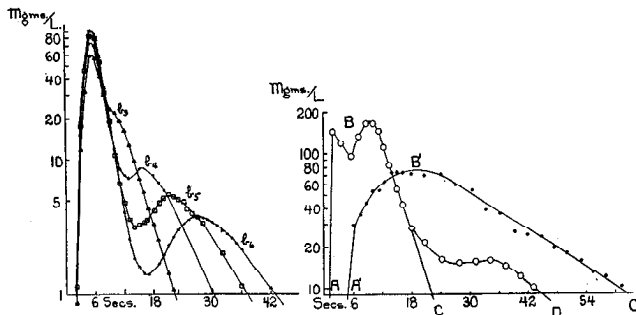


Fig. 2

Fig. 3

Fig. 2. Concentration curves when flow and volume have different relations in two parallel systems.

Fig. 3. The effect of mixing on the concentration curve. *ABD* samples taken from *d*, figure 1; *A'B'C'* samples taken from *f*, figure 1.

curve which would be impressed by volume flow discrepancies that conceivably might (though they probably do not) occur in the lungs.

In animal experiments it is impossible to determine by inspection of the first circulation curve whether the curve follows the simple single system type or the more complicated type illustrated in figure 2, because it is impossible to determine whether there is a bend in the curve below the point (1, 2, 3) where the concentration begins to increase because of the recirculation of the dye.

Since, however, the injection method gives output figures which check very closely with direct Fick output figures (3) and since these injection figures are based on the assumption that the line does continue straight, the inference is that this assumption is correct.

In order to satisfy ourselves that the ± 10 per cent variation inherent in the results of both methods has not hidden some small systematic error

in the injection procedure, we decided to submit it to further checks (7) with heart-lung perfusion experiments.

HEART-LUNG PERFUSION EXPERIMENTS. *Statement of the problems.* The questions that arose in our minds were as follows:

1. Do the mathematical relationships, which we have referred to above as giving rise to the "straight line," hold when the dye is injected into blood which is perfused through the lungs of an animal?

2. Does dye diffuse through the walls of the lung capillaries in sufficient amounts to distort the relationship between the curve and the true flow?

3. Do these mathematical relationships hold when the lung and left heart alone are perfused without the additional margin of safety furnished by the further mixing which might be expected to occur in the great veins, right heart and arteries?

TABLE 2

Comparison of measured flows and volumes with those calculated from figure 3

	MEAS- URED	CALCU- LATED FROM CURVE A B D	CALCU- LATED FROM CURVE A B C	CALCU- LATED FROM CURVE A' B' C'
Flow:				
Cc./min.....	990	1,011	1,245	976
Error, per cent.....		+2.2	+25.7	-1.4
Volume:				
Without H.....	215	235	153	
With H.....	470			480
Error, per cent.....		+9.3	-28.8	+2.0

4. Do they hold whether the flow is slow in relation to the volume, as in human heart disease, or whether the flow is rapid in relation to the volume?

5. Is it possible to obtain any evidence that the quantity V , as calculated, is of the right order of magnitude in animal experiments?

The procedure used in the heart-lung perfusion experiments designed to answer these questions was as follows: About one liter of blood was taken from the hearts of two or three large dogs kept for the purpose. This was heparinized, set aside in a well paraffined flask and kept warm. A small dog—three to five kilos—was bled to death and the blood added to that in the flask. The chest of the small dog was opened, a cannula opening toward the lungs was inserted in the pulmonary artery and one opening toward the heart was inserted in the aorta in such a way as to close the coronaries. The first cannula was connected to a perfusion reservoir by a large vaselined tube 10 mm. in diameter. A 50 cc. glass bulb to take the place of the right heart was inserted between the tube and the cannula. The aortic cannula

was connected to a receiving reservoir by means of a similar tube. The capacities of the tubes, cannulae and bulb were measured.

The lungs were then kept inflated to the size of the chest and perfused several times with the heparinized blood, the flow being regulated to that desired in the particular experiment. Less blood was recovered after the first one or two perfusions, than was originally in the reservoir, indicating that the heart and lungs, under the experimental conditions, contained more blood than immediately after the animal was bled to death. Back pressure in the left ventricle was low; there was no evidence that blood escaped through the Thebesian vessels.

After several perfusions, the kymograph was made ready to receive consecutive timed samples (4) from a needle stuck in the rubber tube as near the aortic cannula as possible. Perfusion was then started and the injection made just above the bulb in the perfusion channel. The samples were set aside to settle and the mixed blood in the receiving cylinder sampled. This procedure was repeated, another injection made and another set of samples taken. The blood was perfused twice more and another sample of the mixed blood set aside. The dye remaining in the blood from the first experiment gives a concentration figure which must be subtracted from each individual determination of the second experiment.

The dye used in these first experiments was usually phenoltetraiodophthalein. This shows a deep blue color in alkali, but remains colorless in serum or water. Brilliant Vital Red, on the other hand, shows its full color in serum or water. Advantage can be taken of this fact to compare successive experiments by injecting into the same perfusing blood first phenoltetraiodophthalein and then Brilliant Vital Red. The serum from the first is diluted with weak alkali and from the second with water.

The experiment was therefore repeated getting samples for two more curves using vital red instead of phenoltetraiodophthalein. Vital red samples were also taken from the receiving reservoir after each perfusion and a sample of the mixed blood taken, two perfusions after the last injection.

From the time-concentration relations of the consecutive samples we were able to plot the curve (see fig. 4) of concentration change from which we could calculate the flow (F) and the width of the intrathoracic vascular bed (V). F could be checked by measuring the flow with a stop-watch and cylinder, and some notion of the accuracy of V could be obtained by comparing the concentration of dye in the receiving chamber with that in the sample taken after the dye had mixed with all the blood in the dog, tubes and reservoirs.

Mathematical relationships. As seen from figure 4, the downstroke of the time-concentration curve in blood perfused through a dog's lung pursues the "straight" course assumed in the discussion.

Diffusibility of the dye. As seen from table 3, the results with phenoltetraiodophthalein differ widely from those with vital red. This is probably due to the diffusion of the former into the tissues for the amount of dye

TABLE 3

Comparison of the measured flow of blood perfused through dog's lungs, with the flow calculated from the results of the injection method using 100 mgm. brilliant vital red and 200 mgm. phenoltetraiodophthalein

PHENOLTETRAIODOPHTHALEIN			VITAL RED		
Observed flow	Calculated flow	Difference	Measured flow	Calculated flow	Difference
<i>cc.</i>	<i>cc.</i>	<i>per cent</i>	<i>cc.</i>	<i>cc.</i>	<i>per cent</i>
120	170	+41.6	948	946	-0.2
237	355	+50.0	1,150	1,092	-5.1
1,118	888	-20.6	1,170	992	-15.2
1,034	952	-7.9	678	621	-8.4
1,325	1,910	+44.1	882	961	+9.0
1,375	1,840	+34.0	600	612	+2.0
690	900	+30.0	882	998	+13.1
662	853	+29.0			
864	1,100	+27.3			
676	733	+8.4			
769	980	+27.3			
Average.....		+23.9	Average.....		-0.7

TABLE 4

Comparison of phenoltetraiodophthalein with brilliant vital red in determining the human cardiac output by the injection method

CASE	PHENOLTE- TRAIODO- PHTHALEIN OUTPUT	BRILLIANT VITAL RED OUTPUT	DIFFERENCE
	<i>L/mm.</i>	<i>L/mm.</i>	<i>per cent</i>
Normal C. V. system.....	7.17	6.76	+6.0
Normal.....	8.88	7.11	+25.0
Angina pectoris.....	6.83	6.61	+3.4
Rheumatic aortic regurg. slightly decom- pensated.....	9.03	7.61	+18.5
Luetic heart compensated.....	4.56	4.40	+3.6
Average.....			+11.2

recoverable in the perfusate was usually lower than expected (-33.5 per cent, -25 per cent, -27 per cent, -18.5 per cent, -14 per cent). In some cases all of the dye could be recovered, which we explain as due to complete washing back of the dye into the blood during the latter part of the perfusion.

Since Brilliant Vital Red is much less diffusible than is phenoltetraiodophthalein; since it was recovered completely in the perfusate; and since the output figures agree quite closely with the measured rate of perfusion, we are convinced that with the vital red dye the determinations actually do measure the output of the heart.

Table 4 indicates that in man there is less difference between the phenoltetraiodophthalein results and the vital red results than one would have been led to expect on the basis of the result of the dog experiments. The error (of the phenoltetraiodophthalein figures) is small enough to have been covered by the inaccuracies of the injection and direct Fick method in the experiments where these have been compared (2, 3). The larger differences between the figures from the two dyes in the perfusion experiments are no doubt due to the fact that the conditions of the experiment increase the permeability of the lung capillaries so as to let out more phenoltetraiodophthalein but not enough to let out the vital red.

The effect of mixing. Although the phenoltetraiodophthalein curves did not always present "straight" downstrokes (on account probably of washing back into the blood stream of dye which had diffused into the capillary walls) the vital red curves were always straight. This was true whether the dye was injected in front of or behind the bulb, so as to have or not to have mixing comparable to that which occurs in the right heart in animal experiments.

The effect of different relationships between flow and volume. Figure 4 shows three types of curves. In the steepest, the flow is rapid in relation to volume, as in normal man and animals; in the intermediate curve, the flow is slower in relation to volume as in dogs under the influence of morphine; and in the flattest, the flow is very slow in relation to volume, as in cases of cardiac decompensation. In all three cases, the downstroke is a straight line, and the flow is calculated accurately. Since the curves from living animals correspond, until recirculation begins, with these curves, and since these curves are of the type which can be used in calculating the output and volume, they confirm us in our belief that the method is usable under a wide variety of conditions.

Estimation of volume in such a way as to check, in these experiments, the calculation based upon mean circulation time and flow, has proved very unsatisfactory. The presence of stagnating blood in the lungs (8, 9, 10) makes any modification of the Welcker method inapplicable, since the latter measures total blood volumes, while we are interested here in actively circulating blood volumes. Figures derived from comparing the dilution of the dye before and after it had mixed with the blood in the dog (see above) were variable and could at best be said to be not inconsistent with the figures derived from the mean circulation time.

CONCLUSIONS AS TO THE NATURE OF BLOOD FLOW THROUGH THE LUNGS.

From what has already been said, it can be gathered that multiplying the mean circulation time by the flow gives only the volume of actively circulating blood in the lungs. What blood remains stagnant in the lungs (an emergency reserve perhaps) (10) is not mixed with the dye and is hence not in the calculation.

One would expect that, since there is stagnant blood in the lungs, there would also be blood moving very slowly. From the above analysis, however, this blood is accounted for by simple prolongation of the time out to infinity or, for practical purposes, to some arbitrarily chosen figure. In other words, when the lungs are perfused, there is no evidence of two or more systems in which the volume flow relationships are different. In all

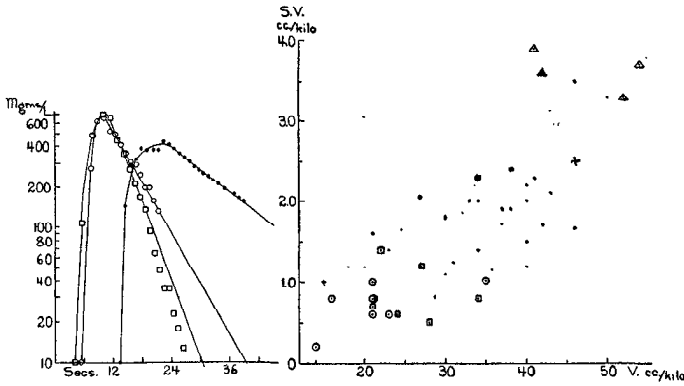


Fig. 4

Fig. 5

Fig. 4. Concentration curves of Brilliant Vital Red in blood perfused through the lungs of dogs.

Fig. 5. Relationships between stroke volume and intrathoracic blood volume in normal dogs, •; in morphinized dogs, Δ ; dogs in hemorrhagic shock, \circ ; and dogs under the influence of barbiturates, \square .

parts of the lung, the amount of blood led into it through the artery is nicely adjusted to the volume of the active vascular bed of that part. If the volume of the vascular bed in the left lung is three-fourths of that in the right lung, the flow to the left lung must be three-fourths of that to the right; otherwise the concentration curve would not be a "straight line." These nice adjustments of flow to volume do not exist in the peripheral vascular bed. One might expect this because of the varying vasomotor reactions in different parts of the peripheral system. Vasoconstriction will cut down the flow to a certain muscle or skin area without encroaching equally upon its vascular volume. When one takes consecutive samples from a superficial arm vein instead of following the usual procedure of arterial puncture, one finds that the concentration does not give a curve

resembling those discussed so far, but one that fluctuates up and down in quite an irregular manner.

ANALYSIS OF "V" FROM THE PHYSIOLOGICAL AND PATHOLOGICAL STAND-POINT. In the animal body, the factor V as calculated by multiplying the mean circulation time by the flow has a meaning which must be carefully defined. The experiments are usually performed so that the dye enters the portals of the heart immediately. In the dog the injections are made into the jugular. Experiments show (1, 3) that the dye is in the right ventricle in normal animals in one or two seconds. Similarly in normal man, injections are made into the antecubital vein of the upraised arm. The dye is seen to descend to the axilla as a "bolus" almost instantaneously and must enter the heart in normal man very soon thereafter. In the normal subject, then, the quantity V has an "anterior" or venous boundary at the point where the injected dye ceases to fall down the collapsed vein and mixes with the main stream. Anatomically this would be at the head of the column of blood raised by the venous pressure somewhere near the base of the axillary vein or in the subclavian. On the venous side V would include more than this. It would also include the blood in all the other great veins that reaches the heart in less time than it takes the median portion of the dyed blood to get there.

The venous boundary of V in the case of decompensation with markedly increased venous pressure would extend out the arm to the top of the column of blood supported by the increased venous pressure and to analogous points in the other branches of the venous tree. Blumgart and Weiss (11) have shown that the circulation time from the arm vein (arm in horizontal position) to the heart is increased in cases of decompensation. This would probably be true, but to a much less extent, when the arm is upraised and if so, would make V extend further out the venous tree in these cases than in normal cases.

On the arterial side V , would include all the blood out to the point of puncture and all the blood that gets out the other branches of the arterial tree in less time than it takes the (median) dyed blood to reach the sampling point. Between the arterial and venous boundaries of V are, of course, the right and left auricles and ventricles, and all of the actively circulating blood in the lungs.

The physical boundaries of V as we have defined them, are necessarily vague. Moreover, conditions which would cause the relative speeding or slowing of flow of one or more arteries or veins make these boundaries variable.

Our conception at the present time is that change in the blood capacity of the lungs is by far the most important cause for change in V . Thus certain decompensated cases which we have studied show a V increased from a normal of two liters to a value of four liters. Since there is probably

a relatively small increase in the vein (upright arm) to heart time, practically none in the left heart to artery time, and a great increase in the pulmonary circulation time (11), one is justified in assuming that the increased V is primarily due to pulmonary congestion.

In order to understand the situation, let us analyze the sequence of events involved in an increase of V . In dogs V usually increases when the heart rate is slowed, either spontaneously or under morphine. Since these conditions do not necessarily reduce the output, there is usually an increase in stroke volume. The essential correlation is, we think, one

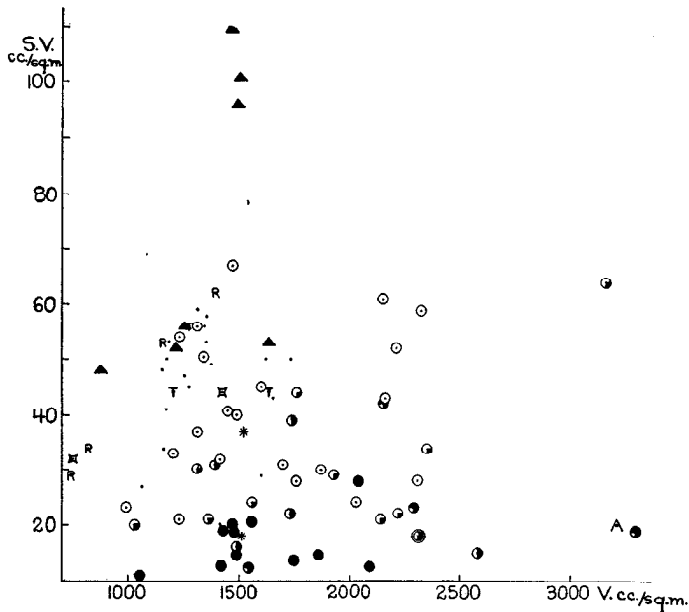


Fig. 6. Relationships between stroke volume and intrathoracic blood volume in man; normal •; cardiac decompensation ◯ ● (the amount of blocking indicates the degree of decompensation); compensated cardiac cases ○; hyperthyroidism, *T*; Raynaud's disease, *R*; pernicious anemia ▲.

between large stroke volume and increased V in normal individuals, and large diastolic size and increased V in the decompensated as well as the normal. This correlation is due to the increased pressure which it takes to fill the heart to the increased diastolic size. This increased pressure causes a congestion of the great systemic veins and an increase in the venous boundaries of V . The left heart also increases its diastolic size and there is here also a necessary increase in the filling pressure. To be effective, it must be transmitted from the right heart through the lung capillaries to the left heart. The studies of Drinker and his collaborators (12, 13) have substantiated the belief that the lung capillaries are subject

to remarkable increases in capacity by passive distention. On this basis, then, the increase in pressure which is necessary to increase the diastolic size of the heart (to increase the stroke volume in normal animals) is necessarily accompanied by an increase in the capacity of the lungs for blood and a decrease in their capacity for air (10, 12).

Increases in heart rate, on the other hand, which result from emotional excitement and are not accompanied by an increased output per minute, or even more strikingly, increases in heart rate from hemorrhage which are accompanied by a marked decrease in output, are both associated with a diminished stroke volume. Looked at from the above point of view, this reduced diastolic size (reduced stroke volume in normal animals) results from a decreased filling pressure on both sides of the heart. The consequences on the right side would involve a movement of the venous bound-

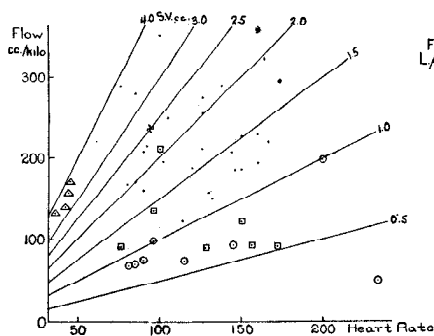


Fig. 7

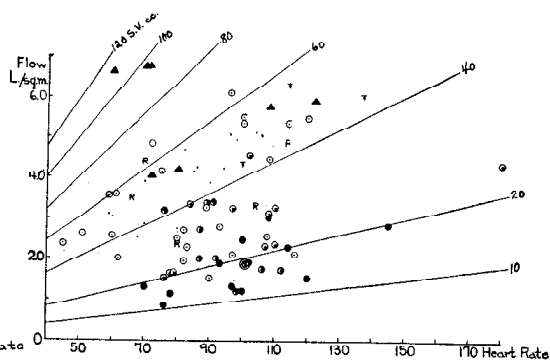


Fig. 8

Fig. 7. Relationship between stroke volume, heart rate and cardiac output in dogs. Symbols as in figure 5.

Fig. 8. Relationship between stroke volume, heart rate and cardiac output in man. Symbols as in figure 6.

aries of V toward the heart, since the veins would be less engorged and the top of the column of blood supported by the venous pressure would not be so high. The difference on the left side would inevitably be greater. The elastic lung capillaries would tend to empty their contents against the decreased filling pressure of the heart and V would be reduced by this factor also.

Illustrative data. In confirmation of this way of looking at the situation we have the results of certain dog experiments, plotted in figure 5 so as to show the relation between stroke volume per kilogram and V per kilogram. In the morphinized dogs Δ the large stroke volume is correlated with a large volume of blood in the heart and lungs (V). Several dogs after hemorrhage \circ and dogs which have been drugged with amytal and barbital \square show both stroke volume and the quantity V decidedly diminished. The normal undrugged dogs \bullet are intermediate in position.

It is to be emphasized that, except for the natural scatter of the observations, the points in figure 5 group around a single correlation line. Factors which increase the stroke volume increase the intrathoracic blood volume.

When these same quantities are plotted (on a surface area basis) for man in normal and pathological conditions, figure 6, two groups are manifest. The first group includes those with normal cardiac function (\bullet normal, \blacktriangle pernicious anemia, R Raynaud's disease (14), T hyperthyroidism). In the second group \circ \bullet are the decompensated cases of cardiac disease. The amount of blocking indicates the degree of decompensation. An intermediate position is occupied by the cases \circ which have more or less regained their compensation. The decompensated group is characterized by a small stroke volume in relation to the amount of intrathoracic blood. The filling pressure of the right heart (venous pressure) is increased in decompensation. An increase in V is an index to the increase in the filling pressure of the left heart which would be expected to, and apparently does, accompany congestive circulatory failure.

In regaining compensation, the stroke volume may increase or remain fairly constant. The intrathoracic blood volume may decrease or not. The essential change seems to consist in assuming a more nearly normal relation between stroke volume and intrathoracic blood volume. There must be a reduction of diastolic size and hence of the filling pressure necessary for an adequate stroke volume.

In figures 7 and 8, the symbols are the same as in the preceding figures. The sectors indicate categories of stroke volume. The ordinates are cardiac output per minute and the abscissae are heart rate. In the dogs, heart rate has no evident relation to either stroke volume or output per minute. There is a tendency for the stroke volume of the dogs in hemorrhagic shock and under barbiturates to remain constant in spite of increases in heart rate. The same can be said of the normal human under our conditions. Nearly all of these subjects had a stroke volume per square meter between 40 and 60 cc. in spite of heart rates ranging from 60 to 120 beats per minute. This application of this principle—due to Henderson—must be restricted, as far as our data go, to subjects at rest and in the recumbent posture. What the findings will be under other conditions must await further information. In the cases of congestive failure it will again be noticed that there is little correlation between heart output and clinical condition. Cases with severe symptoms of the type which are usually referred to congestive circulatory failure may have larger outputs than those whose clinical condition shows marked improvement. How far this may be due to the entrance into the picture of non-cardiac symptoms which simulate those of failure and render the cardiac picture worse than it really is, and how far the actual mechanism of congestive failure is

in fact tied up with cardiac output per se, are problems of a most fundamental and difficult nature. They must await further experiment and detailed clinical analysis.

SUMMARY

1. A mathematical equation is evolved (IV) which expresses the relationship between blood flow, the actively circulating intrathoracic blood volume and the descending limb of the time-concentration curve of an injected dye in successive arterial samples.

2. This equation contains a term, X , which cannot be directly deduced from the above mentioned time-concentration relationship and describes the degree of mixing between the dye and the actively flowing blood in the thorax. Consequently, the flow through and the volume of the system must be calculated from the time-concentration curve using separate formulae which are given in the text (III, V, VI).

3. It is shown that the volume of actively circulating intrathoracic blood cannot be calculated from the fastest circulation time. The time figure which should be used is obtained by measuring the time between the middle of the injection period to the center of gravity of the time-concentration curve.

4. Experiments with glassware show that if the flows through two parallel systems are each in the same proportion to their effective capacity, samples of the mixed outflow give a time-concentration curve whose descending limb conforms to equation IV. If the flow through one bulb is greater in proportion to its effective capacity, the time-concentration curve of the mixed outflow becomes a complicated summative curve whose nature cannot be analyzed under the limitations of physiological experimentation.

5. This situation is analyzed in detail and it is shown that if bulbs are put in series before and after the bulbs in parallel (in the position of the heart in relation to the lungs), the calculations of volume and flow are facilitated.

6. When the lungs and one ventricle are perfused with blood, the injected dye is washed out quite in accordance with equation IV; therefore, in each of the parallel systems in the lungs (lungs, lobes, lobules) there must be the same ratio between effective volume and flow.

7. It is shown that when vital red is used as the injected substance, no appreciable dye diffuses through the walls of the lung capillaries and that the measured perfusion rate checks very closely with that calculated from the time-concentration relations of the dye in the perfused blood.

8. The quantity V is analyzed in detail as to its changing anatomical boundaries, its physiological relationships to cardiac filling and pulmonary congestion under various physiological and pathological conditions. Illus-

trative data are presented from 50 odd experiments on normal unanesthetized dogs, morphinized dogs, and dogs in conditions of circulatory shock as well as from 80 odd experiments on normal and ailing man.

BIBLIOGRAPHY

- (1) HAMILTON, W. F., J. W. MOORE, J. M. KINSMAN AND R. G. SPURLING. 1928. This Journal, lxxxiv, 338.
- (2) HAMILTON, W. F., J. W. MOORE, J. M. KINSMAN AND R. G. SPURLING. 1928. This Journal, lxxxv, 377.
- (3) MOORE, J. W., J. M. KINSMAN AND W. F. HAMILTON. 1929. This Journal, lxxxix, 331.
- (4) KINSMAN, J. M., J. W. MOORE AND W. F. HAMILTON. 1929. This Journal, lxxxix, 322.
- (5) STEWART, G. N. 1897. Journ. Physiol., xxii, 159. 1922. This Journal, lvi, 27.
- (6) BLUMGART, H. L. AND S. WEISS. 1927. Journ. Clin. Invest., iv, 173, 399.
- (7) HAMILTON, W. F., J. W. MOORE, J. M. KINSMAN AND R. G. SPURLING. 1930. This Journal, xciii, 654.
- (8) HAMILTON, W. F., J. W. MOORE AND J. M. KINSMAN. 1927. This Journal, lxxxii, 656.
- (9) HAMILTON, W. F., M. C. SPRADLIN AND H. G. SAAM, JR. 1930. Journ. Physiol., lxx, 344.
- (10) HAMILTON, W. F. AND A. B. MORGAN. In press.
- (11) BLUMGART, H. L. AND S. WEISS. 1928. Journ. Clin. Invest., v, 379.
- (12) DRINKER, C. K., F. W. PEABODY AND H. L. BLUMGART. 1922. Journ. Exper. Med., xxxv, 77.
- (13) DRINKER, C. K., E. D. CHURCHILL AND R. M. FERRY. 1926. This Journal, lxxvii, 590.
- (14) SPURLING, R. G. AND F. JELSMA. Surg., Gyn. and Obst., in press.
- (15) BLUMGART, H. L. Personal communication.