A Method for Measuring the Peripheral Blood Flow by Para-aminohippurate

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Owing to the recent advances in medicine, we have now methods for estimating the volume of the blood flow in many important organs.

As to the blood flow in peripheral regions two kinds of method were reported: the one consists in applying the plethysmography, by which Barcroft *et al.*,¹⁾ Goetz²⁾, Burch³⁾ and Ishikawa *et al.*⁴⁾ and others have studied, and the other consists in using the radioactive isotope Na²⁴, by which Smith *et al.*⁵⁾ and Kety⁶⁾⁷⁾ have studied.

By the method of plethysmography the volume of the blood flow usually can not be estimated numerically, and in many reports by this method, for example in that of Ishikawa *et al.*⁴⁾, numerical volume of the blood flow has not been demonstrated and has been only compared with normal range qualitatively, not quantitatively. This can be said about the report of Smith *et al.*⁵⁾ also.

And so it is thought that some problems lie unsolved in the estimation of the blood flow in peripheral regions, so we will report here a method for measuring the peripheral blood flow quantitatively by PAH, although it also contains one assumption, which must be clarified in future.

THEORETICAL CONSIDERATION

Fig. 1 is a scheme expressing the arteries and veins in one region of a body.

When C represents the PAH concentration in the arteries in the region under PAH equilibrium and F the volume of the plasma flowing into the region in one minute, that is, the plasma flow, then the volume of the PAH, which flows into the region from time 0 to t is expressed as follows:

$$\int_0^t FCdt = F \int_0^t Cdt \quad (1)$$

On the other hand, the flow out of the region occurs through veins

Fig. 1. A scheme of the arteries and veins in a region of a body. C and c represent the PAH concentration in the arteries and veins respectively and F represents the plasma flow per minute in the region.

and lymphatics. Because the PAH concentration can be thought to be approximately equal in the veins and lymphatics in the region under PAH equilibrium as explained later, the volume of the PAH, which is carried away out of the region is expressed as follows, when c represents the PAH concentration in the veins.

$$\int_0^t F c dt = F \int_0^t c dt \quad (2)$$

According to Schwartz⁹⁾ PAH enters into tissue cells, but as we⁹⁾ reported previously, the PAH, which entered into tissue cells, is thought not to flow easily out of the cells into interstitial fluid, and therefore the PAH in the cells can be thought to have no relation to PAH equilibrium.

Now, when the plasma volume in the arteries and veins (the plasma volume in the veins includes in this report the volume of the fluid in the lymphatics) and the volume of the interstitial fluid in the region are represented by A , V and G respectively, and the PAH concentrations in the arteries, veins and interstitial fluid in the region at time 0 are represented by C_0 , c_0 and C_{G0} respectively and at time t by C , c and C_G , the following equation can be obtained from (1) and (2) by Fick's principle.

$$F \left\{ \int_0^t c dt - \int_0^t C dt \right\} = A(C_0 - C) + V(c_0 - c) + G(C_{G0} - C_G) \quad (3)$$

As reported previously¹⁰⁾¹¹⁾ the PAH concentration in arteries is smaller than that in veins and the logarithms of each concentration are expressed by two parallel straight lines against time as drawn in Fig. 2, and when the direction co-efficient of these lines are represented by $-\alpha$, each straight line can be expressed by such equations as written in Fig. 2. Therefore

$$\left. \begin{aligned} C &= C_0 10^{-\alpha t} \\ c &= c_0 10^{-\alpha t} \end{aligned} \right\} \quad (4)$$

Therefore

Fig. 2. Relation of logarithms of PAH concentrations in artery and vein to time. C_0 and c_0 represent the PAH concentration in artery and vein respectively at time 0, and C and c at time t . And $-\alpha$ represents the direction co-efficient.

$$\frac{C}{c} = \frac{C_0}{c_0}$$

That is, the ratio of the PAH concentration in arteries to that in veins is kept constant at each time. Under PAH equilibrium PAH is excreted in the kidneys and the PAH concentrations in arteries and veins decrease with time, and so in order to keep equilibrium, PAH is thought to continue to flow into veins from interstitial fluid corresponding to the difference between the PAH concentrations in veins and interstitial fluid. So, because the ratio of the PAH concentration in arteries to that in veins is constant at each time, the PAH concentration in interstitial fluid must have a constant ratio to that in arteries and/or veins. And so the logarithm of the PAH concentration in interstitial fluid must make a straight line against time, the direction co-efficient of which is also $-\alpha$. Therefore

$$\ln C_G = \ln C_{G0} - \alpha t$$

Therefore

$$C_G = C_{G0} 10^{-\alpha t} \quad (5)$$

From (3), (4) and (5)

$$F \left\{ \int_0^t c_0 10^{-\alpha t} dt - \int_0^t C_0 10^{-\alpha t} dt \right\} = AC_0(1 - 10^{-\alpha t}) + Vc_0(1 - 10^{-\alpha t}) + GC_{G0}(1 - 10^{-\alpha t}) = (1 - 10^{-\alpha t})(AC_0 + Vc_0 + GC_{G0}) \quad (6)$$

And $\int_0^t 10^{-\alpha t} dt = \frac{1 - 10^{-\alpha t}}{\alpha \log_e 10}$, so (6) becomes as follows:

$$F \cdot \frac{(1 - 10^{-\alpha t})(c_0 - C_0)}{\alpha \log_e 10} = (1 - 10^{-\alpha t})(AC_0 + Vc_0 + GC_{G0}) \quad (7)$$

Because the PAH concentration in arteries and consequently in veins decreases with time due to the excretion of PAH in the kidneys, PAH, as explained above, flows continuously from interstitial fluid into veins to

keep equilibrium, and the fact, that PAH concentration in veins is usually greater than that in arteries considerably, means that a large volume of PAH has moved into veins out of interstitial fluid, that is, that PAH can move freely and rapidly between capillaries and interstitial fluid, and therefore the PAH concentration in interstitial fluid will be almost equal to or only a little greater than that in veins, and the difference between these two will be very slight, compared with the difference between the PAH concentrations in veins and arteries.

On the other hand, comparing the volume of interstitial fluid with that of the plasma in arteries, the former is much greater than the latter, and according to Hernandez-Peón¹²⁾ the volume of interstitial fluid occupies 13.2% of body weight, and that of plasma 4.3%. If this rate can be applied to the region in question, the volume of the interstitial fluid in the region G is three times the volume of the plasma in the region and therefore it can be thought to be greater than three times the volume of the plasma in the arteries in the region A, perhaps to be equal in approximation to six or seven times A or more.

And as explained above, the difference between the PAH concentrations in the interstitial fluid and veins will be much smaller than that between the veins and arteries in the region, and comparing these differences with each other at time 0, $C_{G0} - c_0$ will be much smaller than $c_0 - C_0$, and perhaps the latter may be assumed to be six or seven times the former or more. Therefore, even if we assume that the following formula will exist in approximation, there may not occur a great error.

$$A(c_0 - C_0) \doteq G(C_{G0} - c_0)$$

Therefore

$$AC_0 + GC_{G0} \doteq Ac_0 + Gc_0 \quad (8)$$

From (7) and (8)

$$F \cdot \frac{(1 - 10^{-\alpha t})(c_0 - C_0)}{\alpha \log_e 10} = (1 - 10^{-\alpha t})(A + V + G)c_0$$

According to Schwartz⁸⁾ and Schwartz *et al.*¹³⁾ mannitol-, inulin- and thiosulfate-spaces correspond to the volume of the extracellular fluid and PAH-space is greater than those spaces. This means that a part of PAH enters into tissue cells and the other part is distributed in all the extracellular fluid. As explained above, the PAH which entered into tissue cells has no relation to PAH equilibrium, and so the PAH-space which has relation to it can be thought to be equal to the volume of the extracellular fluid. Although $(A + V + G)$ is the PAH-space relating to the PAH equilibrium, it will correspond in approximation to the volume of the extracellular fluid ECF in the region. Therefore the following formula can be obtained.

$$\frac{F}{ECF} = \frac{\alpha c_0 \log_e 10}{c_0 - C_0} = \frac{2.303 \alpha c_0}{c_0 - C_0} \quad (9)$$

$\frac{F}{ECF}$ in (9) is the volume of plasma flow per 1 cc. of extracellular fluid in the region per minute. So the volume of the plasma flow per 100 cc. of extracellular fluid in the region per minute is represented by the following formula.

$$\frac{F}{ECF} \times 100 = \frac{2.303 \alpha c_0}{c_0 - C_0} \times 100 \quad (10)$$

EXPERIMENTAL METHOD

The data, which were used in the present study, are those, which had been gotten on 32 normal and hypertensive individuals in the two studies reported previously as "A Method of Measuring the Volume of the Circulating Blood in the Lungs and the Minute Volume by Means of Sodium Para-aminohippurate"¹⁰ and "On the Measurement of the Respective Volumes of the Circulating Blood in Arteries and in Veins."¹¹ Using these data we calculated the volume of the plasma flow per 100 cc. of extracellular fluid per minute from (10). In these previous experiments we took three blood samples from femoral artery as well as from antecubital vein between 30 and 50 minutes after intravenous injection of 2000 mg. of PAH as previously reported, and estimating the PAH concentration in these six samples we got two parallel straight lines, which the logarithms of the PAH concentrations in the artery and vein made against time.

Because the PAH concentration is equal in all arteries, the value of $\frac{F}{ECF} \times 100$, which is calculated from (10) is the volume of the plasma flow per minute per 100 cc. of extracellular fluid in the forearm of the side, on which the venous blood was taken for samples. And we calculated the renal plasma flow, adopting 88% as extraction rate according to Warren *et al.*¹⁴

EXPERIMENTAL RESULTS AND DISCUSSION

In Table I and II we present the values of the plasma flow per 100 cc. of extracellular fluid in a forearm, renal plasma flow and, in cases where blood pressure has been estimated, the values of blood pressure and mean arterial pressure (diastolic pressure + $\frac{1}{3}$ pulse pressure), on 22 normal and 10 hypertensive individuals. In this report we included two cases No. 24 (blood pressure 146/94, mean arterial pressure 111) and No. 25 (blood pressure 140/94, mean arterial pressure 109) in hypertension, which had

TABLE I
Values of Peripheral Plasma Flow, Renal Plasma Flow,
Blood Pressure and Mean Arterial Pressure

$\frac{F}{ECF} \times 100$ represents the plasma flow per 100 cc. of extracellular fluid in forearm per minute, and RPF, BP and MAP represent the renal plasma flow, blood pressure and mean arterial pressure respectively, in normal individuals.

No.	Age	Sex	Diagnosis	$\frac{F}{ECF} \times 100$ (cc.)	RPF (cc.)	BP	MAP
1	30	♂	normal	18.8	587		
2	23	"	"	16.0	563		
3	29	"	"	8.7	451		
4	37	"	"	20.5	554		
5	41	"	"	10.1	679		
6	30	"	"	8.7	241		
7	27	"	"	15.1	676		
8	27	"	"	8.0	622		
9	29	"	"	11.9	870		
10	24	"	"	12.1	877		
11	22	♀	"	14.2	635		
12	22	"	"	25.3	693		
13	29	"	"	22.6	661		
14	35	♂	"	18.2	706	116/78	91
15	40	"	"	15.6	657	120/70	87
16	43	"	"	13.2	875	132/80	97
17	26	"	"	14.9	681	124/60	81
18	29	"	"	13.5	708	124/70	88
19	45	"	"	17.3	498	126/76	93
20	38	"	"	19.1	413	120/0	40
21	62	"	"	16.7	602	112/80	91
22	41	"	"	14.8	807	130/80	97
Mean				15.2			

been reported previously as normal.

As shown in tables the plasma flow per 100 cc. of extracellular fluid in the forearm per minute is 8.0–25.3 cc. (mean 15.2 cc.) in normal and 11.9–36.1 cc. (mean 18.3 cc.) in hypertensive individuals. Barcroft *et al.*¹⁾ reported 2–7 cc. as the blood flow per 100 cc. of tissue of the forearm estimated by plethysmography. We will compare it with ours.

According to Hernandez-Peón¹²⁾ the volume of the extracellular fluid corresponds to 17.5% of body weight in approximation. And so, if this rate can be applied to the forearm in question, 100 cc. of the extracellular

TABLE II

Values of Peripheral Plasma Flow, Renal Plasma Flow,
Blood Pressure and Mean Arterial Pressure

In hypertensive individuals. For abbreviations see Tab. I.

No.	Age	Sex	Diagnosis	$\frac{F}{ECF} \times 100$ (cc.)	RPF (cc.)	BP	MAP
23	50	♂	Essential Hypertension	16.4	831		
24	54	"	"	11.9	731	146/94	111
25	55	"	"	15.2	609	140/94	109
26	57	"	"	14.5	414	210/120	150
27	58	"	"	23.1	430	180/90	120
28	59	"	"	18.4	697	184/80	114
29	44	"	"	36.1	718	166/90	115
30	65	"	"	16.2	424	176/100	125
31	54	"	"	15.5	579	160/100	120
32	53	"	"	15.9	481	155/90	111
Mean				18.3			

fluid corresponds approximately to 570 cc. of the tissue of the forearm. Consequently, when we convert our values into those for the plasma flow per 100 cc. of the tissue of the forearm, we get as plasma flow 1.4–4.4 cc. (mean 2.7 cc.) in normal and 2.1–6.3 cc. (mean 3.2 cc.) in hypertensive individuals. When we convert these values into blood flow, we get 2.3–7.3 cc. (mean 4.5 cc.) as blood flow per 100 cc. of the tissue of the forearm in normal and 3.5–10.5 cc. (mean 5.3 cc.) in hypertensive individuals in approximation, although we have not estimated hematocrit values. Our values on normal individuals are equal in approximation to those reported by Barcroft *et al.* as 2–7 cc.

Then we will compare our results with Kety's. Kety⁽⁶⁷⁾ injected Na^{24} into gastrocnemius and calculated the value for k from the following formula,

$$k = \frac{\log C_1 - \log C_2}{0.4343(t_2 - t_1)}$$

where C_1 and C_2 equal counts by Geiger-Müller counter per minute at time t_1 and t_2 respectively. And on the other hand, k is represented theoretically by the following formula

$$k = \frac{mF_v}{S} + \frac{nF_L}{S}$$

where S represents sodium space in a small unit mass of the tissue, into which Na^{24} has been injected, F_v and F_L the respective venous and lym-

phatic outflow per minute, and m and n are constants with values between 0 and 1. According to him k , that is, the clearance constant, although not a rigid measure of total blood flow, is an accurate and quantitative measure of the effectiveness of the local circulation including not only blood flow but other mechanisms responsible for local homeostasis. In tissues where diffusion occurs rapidly and is not a limiting factor, the clearance constant approximates the blood flow.

The values for k in 8 cases reported by him are between 0.033–0.066 (mean 0.050). Because Na^{24} is distributed only in extracellular fluid and it is so diffusible that m and n may be equal in approximation to 1, we can assume the values for k equal in approximation to the plasma flow per 1 cc. of extracellular fluid per minute in gastrocnemius, and so the plasma flow per 100 cc. of extracellular fluid per minute is 3.3–6.6 cc. (mean 5.0 cc.) in gastrocnemius, one third our values in forearm. (It must be emphasized that Kety has not performed such a calculation for the reason mentioned above.) This difference between the values obtained by our method and calculated by us from Kety's results seems to depend upon the difference of the region, at which measurement was done, because it seems natural that the blood flow will differ in different organs or tissues.

Sancetta *et al.*¹⁵⁾ have reported 0.0232–0.4226 cc. as the rate of blood flow in the finger per 5 cc. of part per minute determined by the venous occlusion technique of Cranley *et al.*¹⁶⁾ in 8 normal individuals. When these values are converted in the rate of blood flow in the finger per 100 cc. of part per minute, we get 0.46–8.5 cc. (mean 4.8 cc.). Our values for the blood flow per 100 cc. of the tissue in the forearm per minute in normal individuals are 2.3–7.3 cc. (mean 4.5 cc.) as mentioned above, and both values are approximately equal.

By the method reported by Smith *et al.*⁵⁾ and Ishikawa *et al.*⁴⁾ numerical volume of the blood flow can not be obtained.

Comparing our results with those of the authors above mentioned it is supposed that the theory underlying this method will be correct and it can be applied clinically.

Between blood pressure and the blood flow in forearm the relation $R = \frac{P}{F}$ must exist, where R , F and P represent the peripheral resistance, the blood flow and the pressure difference between the mean arterial pressure and the venous pressure, respectively. The venous pressure is said to vary considerably in different individuals, and in hypertension it is usually within normal limits. In these experiments we have not estimated the venous pressure in antecubital vein and also hematocrit values, so we can not know the accurate pressure difference and the volume

of the blood flow, but, because the venous pressure will be very small, when compared with the mean arterial pressure, and the ratio of the plasma flow to the blood flow will be almost constant, the ratio of the mean arterial pressure to the plasma flow can be thought to be proportional to the peripheral resistance. We expected that this ratio would be greater in hypertensive individuals than in normal, but such a relation could not be found. Because the values of the plasma flow in the forearm in hypertensive individuals are slightly greater than normal as shown in tables, there results consequently no increase in the peripheral resistance in the forearm of the hypertensive in spite of increase in the mean arterial pressure. For this, two reasons can be guessed: 1) that in the forearm of the hypertensive there is no constriction of arterioles more than the normal or 2) that, although the arterioles in the forearm constrict to some extent in hypertensive individuals, the constriction of the arterioles in other organs or tissues is more increased than in the forearm and the blood flow in those organs or tissues of greater resistance will be decreased, resulting in increase in the blood flow in the forearm, because it is an accepted fact that the cardiac output is usually of normal value in hypertension. In case No. 27 the renal plasma flow is 430 cc. and the plasma flow in forearm 23.1 cc., and the latter seems to be relatively greater, compared with the former. So it can be supposed that in this case the blood flow in the forearm may be increased passively owing to the decrease in the renal plasma flow, against which the resistance in the kidneys would presumably have been increased. But the extraction rate of PAH in hypertensive individuals, whose kidneys have been injured, is expected to be smaller than in normal, and if so, the real renal plasma flow will be greater than the calculated value. In case No. 29, in which the renal plasma flow and the plasma flow in the forearm are both of great value, it is presumed that the stroke volume and cardiac output will be greater than normal, resulting in hypertension and increase in the plasma flow both in kidneys and forearm, but because we have not estimated it, we can not conclude.

Finally, we did not estimate hematocrit values and venous pressure and the cases studied are few in number, so we can conclude nothing about the hemodynamics in hypertension in this study.

This method is based on the assumption, that in the forearm the relation $AC_0 + Vc_0 + GC_{G_0} \doteq (A + V + G)c_0$ will exist in approximation, and therefore the blood flow can be estimated by this method in any organ or tissue, where the above mentioned assumption will exist, and this method can be applied clinically for estimating the blood flow in peripheral organs or tissues. But it must be clarified in future, to what extent the assumption $AC_0 + Vc_0 + GC_{G_0} \doteq (A + V + G)c_0$, that is, that the mean concentration of PAH in the extracellular fluid is approximately equal to the PAH

concentration in the veins, will exist in organs or tissues in question.

SUMMARY

A method for measuring the volume of the peripheral blood flow by using PAH was reported. The values of the plasma flow per 100 cc. of extracellular fluid in forearm per minute was 8.0–25.3 cc. (mean 15.2 cc.) in 22 normal individuals and 11.9–36.1 cc. (mean 18.3 cc.) in 10 hypertensive, and this method is supposed to be able to be applied clinically for estimating the blood flow in organs or tissues, where the assumption, that the mean concentration of PAH in the extracellular fluid is approximately equal to the PAH concentration in the veins, can exist.

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