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A QUICK METHOD FOR CALCULATION OF THE VASCULAR MEAN TRANSIT TIME

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A simple, quick, and accurate method for the determination of mean transit time (τ) from an arterial bolus injection of a radioactive nondiffusible tracer was derived. In this method the mean transit time is simply equal to the width, in time, of the vascular clearance curve when its height has been reduced to 1/e of the maximum value. Using radioactive $C^{15}O$-hemoglobin as a vascular tracer, τ was calculated by this method (τ_{eq}) and compared with a direct integration method (τ_p) with a planimeter for 52 cerebral τ measurements in rhesus monkeys and humans. The values of τ ranged from 1.4 to 10.7 sec. The regression analysis of the values of τ calculated by the two methods gave the equation $\tau_{eq} = 1.007\ \tau_p + 0.001$, $r = 0.999$, $p < 0.0001$. The method suggested in this work requires a single semilog plot and takes less than a minute whereas the planimeter method requires a semilog and linear plot and takes 10–15 min to calculate τ. There was no demonstrable decrease in accuracy using the suggested method when comparisons were made to the direct integration method (above equation).

A number of radioactively labeled compounds have been employed as nondiffusible vascular tracers in the brain, heart, and kidney to determine the vascular mean transit time (τ). One of the most accurate methods in the measure of the true mean transit time has employed an arterial bolus injection and the external recording of the vascular clearance curve from the organ of interest. The clearance curve can be determined by either the time course of activity in the organ (residue detection) or by measuring the time course of activity leaving the organ (outflow detection). Zierler (*1*), using residue detection, has shown that the mean transit time or first moment of the clearance curve following a rapid arterial bolus injection can be calculated from the clearance curve by $\tau = A/H_0$, where A is the area under the curve and H_0 is the maximum height. The two major assumptions in this method are that H_0 represents the total amount of tracer in the region or organ of interest (no input while there is output), and that the area, A, under the clearance curve represents the clearance of H_0 amount of tracer. The first assumption is upheld by a rapid arterial bolus injection (spike input). The second assumption has to deal mainly with the problem of recirculation. Recirculation in the case of vascular tracer can be dealt with by a Hamilton extrapolation (*2*) in which the monoexponential portion of the clearance curve before recirculation occurs is extrapolated to a near-zero value as shown in Fig. 1. Then τ can be calculated by determining the area under the extrapolated curve and dividing by the height, H_0, of the curve. This can be done by computer analysis. However, in cases where a computer is not available, the area under the curve is determined with a planimeter or a summing technique and obtaining the value of H_0 from the curve. We would like to propose a simple, fast, and accurate technique to perform this calculation.

THEORY OF ANALYSIS

After a Hamilton extrapolation is performed on a clearance curve, it can be split up into three regions as shown in Fig. 1. The regions 1, 2, and 3

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are respectively formed by the upslope from the activity entering the organ, the flat region where the activity is distributing through the organ, and the downslope from the activity that is exiting from the organ. The problem is to determine the area contained within these three regions for the evaluation of the mean transit time by $\tau = A/H_0$.

Area 3 is nothing more than the area under a curve with a monoexponential decay from t_2 to ∞.

$$H_3(t) = H_0 e^{-\lambda_3(t-t_2)} \qquad (1)$$

where the decay constant $\lambda_3 = 1/(1.44\, t_{1/2}^{(3)})$. This area can be found by integrating Eq. 1 from time t_2 to ∞. Thus

$$A_3 = \int_{t_2}^{\infty} H_3(t)dt = \int_{t_2}^{\infty} e^{-\lambda_3(t-t_2)}dt$$
$$= 1.44\, H_0 t_{1/2}^{(3)} \qquad (2)$$

Area 2 is the area of a rectangle, and thus

$$A_2 = H_0(t_2 - t_1) = H_0 T^{(2)} \qquad (3)$$

where $T^{(2)}$ simply equals the length of the flat region of the curve between t_1 and t_2.

Area 1 is the area under a rising exponential function

$$H_1(t) = H_0 e^{\lambda_1(t-t_1)} \qquad (4)$$

where $\lambda_1 = 1/(1.44 t_{1/2}^{(1)})$. The time t_1 is taken at the start of the flat plateau as shown in Fig. 1. The monoexponential assumption of this portion of the curve has no theoretical foundation since it is the leading edge of the bolus of activity as it enters the field of the radiation detector. However, in over 50 cerebral mean transit time determinations in rhesus monkeys and humans reported in this study, we found this to be a good first-order assumption. A_1 can be calculated by integrating Eq. 4 from 0 to t_1. Thus:

$$A_1 = \int_0^{t_1} H_1(t)dt = \int_0^{t_1} e^{\lambda_1(t-t_1)}dt$$
$$= 1.44\, H_0 t_{1/2}^{(1)} (1 - e^{-\lambda_1 t_1}) \qquad (5)$$

If $\lambda_1 t_1$ is large, then $e^{-\lambda_1 t_1}$ is small compared with 1 and can be neglected. If $t_1 \geqq 7\, t_{1/2}^{(1)}$, then $e^{-\lambda_1 t_1}$ is ≤ 0.01. This assumption was found to hold in all the cases presented here. However, A_1 is very small compared with A_2 and A_3 and even an error of 25% ($t_1 = 2t_{1/2}^{(1)}$) would cause about a 1% error in the total area. Thus

$$A_1 \simeq 1.44\, H_0 t_{1/2}^{(1)} \qquad (6)$$

Since the total area is $A = A_1 + A_2 + A_3$, we have

$$A = H_0[1.44\, (t_{1/2}^{(1)} + t_{1/2}^{(3)}) + T^{(2)}] \qquad (7)$$

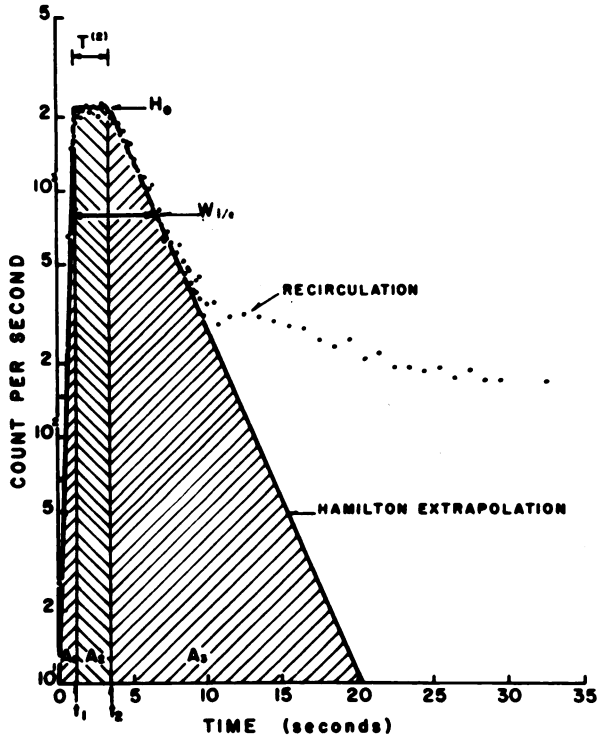

FIG. 1. Vascular clearance of $C^{15}O$-hemoglobin from internal carotid bolus injection in rhesus monkey. $W_{1/e}$ refers to width of clearance curve at height of $H_0/e = H_0(0.368)$.

The mean transit time τ can be calculated from $\tau = A/H_0$ and Eq. 7 to give

$$\tau = 1.44\, (t_{1/2}^{(1)} + t_{1/2}^{(3)}) + T^{(2)} \qquad (8)$$

where H_0 canceled out.

It is easily seen that during the mean time of $1/\lambda$ (which equals $1.44\, t_{1/2}$) the monoexponentials of A_1 and A_3 are decreased to 1/e of their initial value.

$$H = H_0 e^{-\lambda t} = H_0 e^{-\lambda/\lambda} = H_0/e \qquad (9)$$

Since A_2 (rectangle) has the same time duration at any height, then the mean transit time τ can be calculated by determining the width ($W_{1/e}$) of the clearance curve (Fig. 1) at 1/e (1/e = 0.368) of the maximum height H_0. Thus

$$\tau(\text{sec}) = W_{1/e}(\text{sec}) \qquad (10)$$

Equations 8 and 10 are identities.

EXPERIMENTAL METHOD AND RESULTS

Experimental method. Oxygen-15-labeled CO-hemoglobin was used as a nondiffusible tracer for the determination of the cerebral vascular mean transit time. Thirty-four measurements were performed in rhesus monkeys and 18 in human subjects.

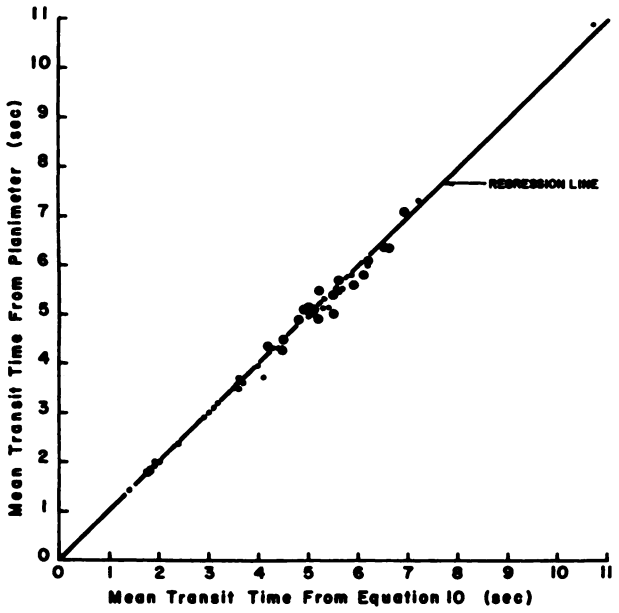

FIG. 2. Plot of cerebral mean transit times from internal carotid injections of $C^{15}O$-hemoglobin calculated by Eq. 10 and planimeter method. Closed and open circles indicate rhesus monkeys and humans, respectively. Solid line is regression equation (Eq. 11 in text).

To facilitate the bolus injection of the $C^{15}O$-hemoglobin into the internal carotid artery of the monkeys, all branches of the right external carotid artery were ligated 2 weeks prior to the experiments. The tracer was then injected as a small bolus (0.2 cc) into the common carotid artery through a catheter inserted from a femoral approach. The duration of the injection was 0.5 sec.

The monkeys were anesthetized with phencyclidine, paralyzed with gallamine, and passively ventilated on 100% oxygen with a Harvard respirator. The vascular mean transit time was varied by hyperventilation, hypoventilation, and administration of admixtures of oxygen and carbon dioxide.

The time course of $C^{15}O$-hemoglobin through the brain was measured by a shielded and collimated 3- × 2-in. NaI(Tl) scintillation detector which was placed in such a manner as to view the injected hemisphere. The signal from the NaI(Tl) detector after narrow pulse-height analysis was recorded by a small on-line digital computer in which corrections were made for radioactive decay and room background. The data were collected at 0.2-, 1.0-, and 5.0-sec consecutive intervals for 10, 20, and 90 sec, respectively.

In the measurements with human subjects a bolus (1.5 cc) of the tracer was injected through a small catheter placed in the internal carotid artery. The duration of the injection was approximately 0.5 sec. The time course of the cerebral clearance curve was measured regionally by three shielded and collimated NaI(Tl) detectors which were placed in such a manner as to view the frontal, parietal, and occipital regions of the brain. The data were recorded by the on-line computer system as described before.

TABLE 1. COMPARISON OF CEREBRAL MEAN TRANSIT TIME (τ) CALCULATED BY EQ. 10 AND A PLANIMETER*

Subject	Number	τ Eq. 10 (sec)	τ Planimeter (sec)
Rhesus monkey	1	4.0	4.0
	2	3.2	3.2
	3	4.3	4.3
	4	1.9	2.0
	5	5.8	5.8
	6	5.4	5.1
	7	5.7	5.5
	8	5.6	5.5
	9	5.1	5.0
	10	3.5	3.5
	11	5.0	5.0
	12	2.9	2.9
	13	3.7	3.6
	14	6.2	6.0
	15	1.8	1.8
	16	3.6	3.6
	17	1.8	1.9
	18	3.6	3.5
	19	5.3	5.1
	20	1.9	2.0
	21	3.1	3.1
	22	1.8	1.8
	23	3.6	3.7
	24	4.1	4.2
	25	1.4	1.5
	26	5.3	5.3
	27	3.0	3.0
	28	2.0	2.0
	29	10.7	10.9
	30	4.4	4.3
	31	1.8	1.8
	32	2.4	2.4
	33	3.6	3.7
	34	7.2	7.3
Human	35	5.1	5.1
	36	5.6	5.7
	37	6.2	6.1
	38	4.8	4.9
	39	5.2	4.9
	40	5.5	5.0
	41	6.1	5.8
	42	4.5	4.5
	43	4.9	5.1
	44	5.5	5.4
	45	5.9	5.6
	46	6.9	7.1
	47	4.2	4.3
	48	6.5	6.3
	49	4.5	4.2
	50	5.2	5.4
	51	6.6	6.3
	52	5.0	5.1

* $C^{15}O$-hemoglobin was used as the nondiffusible blood tracer.

Results. The data from 52 cerebral mean transit time determinations, 34 in monkeys and 18 in humans, were analyzed by Eq. 10, and by calculating $\tau = A/H_0$ in which the area A under the clearance curve, after a Hamilton extrapolation, was determined with a planimeter. The data are listed in Table 1 and shown in Fig. 2. A linear regression analysis of the data yielded the equation

$$\tau_{eq} = 1.007\ \tau_p + 0.001 \quad r = 0.999, p < 0.0001 \tag{11}$$

where τ_{eq} and τ_p are the mean transit times calculated by Eq. 10 and by the planimeter method, respectively. Equation 11 is essentially a line of identity. The average deviation of the two methods was $<2\%$ (1σ).

DISCUSSION AND CONCLUSION

The analysis of the area under the clearance curve by the planimeter method requires a semilog plot, extrapolation, linear plot of extrapolated data, and the tedious integration with the planimeter. This takes about 10–15 min, whereas Eq. 10 requires only the semilog plot and takes less than a minute to calculate τ. Equation 8 is equivalent to Eq. 10, and could also be used to calculate τ, but Eq. 10 is obviously quicker.

It should be pointed out, as Zierler has previously stated (*1*), that the Hamilton extrapolation is only good when recirculation is a relatively late event. The point at which recirculation causes a significant interference must be determined for each particular application.

The approach suggested in this work was validated for cerebral transit times but the method should apply equally well in other organs, such as the heart and kidney, as long as the shapes of the vascular clearance curves are similar to those reported here for cerebral studies. Prolonged arterial or intravenous injection techniques will alter the shape of the curves from those reported in this work and will lower the accuracy of Eq. 10 for the calculation of τ. However, it would also lower the accuracy of any method of assessing τ by A/H_0 unless the variation in the input function is taken into account.

Thus Eq. 10 offers a simple, quick, and accurate method for the determination of τ.

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