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THEORY OF THE MEASUREMENT OF BLOOD FLOW BY THE DILUTION OF AN INDICATOR

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It is shown that the instantaneous concentration of an indicator at one point in a circulation can be related to all previous concentrations at a second point by an integral equation. Solutions of this equation give formulae for the computation of the mean transit time, the flow, and the volume of the circulation between the two points.

Cardiac output has been estimated by injecting a salt or a dye into a vein and measuring its concentration in an artery (Stewart, 1897; Hamilton and Remington, 1947.) This paper presents a theory for the interpretation of such measurements.

It is useful to think of the movement of blood from the left heart as resembling a river which separates into several branches that flow into a like number of swamps, the systemic capillaries. Their drainage forms a single stream which again divides and runs through a second set of swamps, the pulmonary capillaries. However, the flow through the swamps differs from the sanguinous circulation—drainage from the second swamps is to the ocean, but from the pulmonary capillaries drainage is again to the left heart.

Suppose at the moment $t = 0$ we *suddenly* add to the inflow of the swamps an amount M of an indicator I, which stays in the stream. If $f(t)$ is the probability that it takes a particle the interval of time t to traverse the swamps, then the fraction of M flowing out of the swamps at time t will be $f(t)$ and hence the rate of drainage of I from the swamps will be $\frac{dM}{dt} = Mf(t)$ or

$$dM = Mf(t)\,dt\,. \tag{1}$$

If F is the flow through the swamps per unit time, the drainage from the swamps in the time dt is Fdt. Hence the cross-stream average concentration C of I is

$$C(t) = \frac{dM}{Fdt} = \frac{Mf(t)}{F}. \tag{2}$$

Equation (2) can be generalized so as to relate the concentration of I in the drainage, C_2, to the concentration in the inflow, C_1. The fraction of $C_2(t)$ contributed by the inflow at time, $t—\eta$, is

$$dC_2(t) = C_1(t-\eta) f(\eta) d\eta . \tag{3}$$

Integration over all previous time gives

$$C_2(t) = \int_0^\infty C_1(t-\eta) f(\eta) d\eta . \tag{4}$$

Equation (2) does not apply to circulations because it does not account for indicator fed back into the inflow from the drainage, e.g., indicator passing through the system for a second or third time. The quantity C_1 in equation (4) includes all I. Hence equation (4) should be used in calculating the behavior of a circulation.

It is easy to solve equation (4) when I is added to a circulation at a constant rate m. Conceive circulation from X to Y, from Y to Z, and from Z to X. Then Y, the point of addition, is "between" X and Z. The quantity C_1 at X is related to C_2 at Z by

$$C_2(t) = \frac{m\theta(t)}{F} + \int_0^t C(t-\eta) f(\eta) d\eta , \tag{5}$$

where $\theta(t)$, an arbitrary function accounting for transients, increases monotonically, $0 \leqq \theta(t) \leqq 1$.

The average concentration of indicator throughout the circulation at time t is mt/V, where V is the volume of the circulation. Since for capillary beds $f(t)$ is not a delta function* or a sum of delta functions, transients are damped and C at any point approaches $m(t—a)/V$, where a depends on the point of addition.

As $t \to \infty$,

$$C_2(t) \to \frac{m}{F} + \int_0^\infty \frac{m(t-a-\eta)}{V} f(\eta) d\eta \tag{6}$$

or

$$C_2(t) = m/F + C_1(t) - mb/V, \tag{7}$$

*A "delta" function is an impulse function which is defined in the following way:

$$\delta(t - t_0) = \lim_{a \to 0} \frac{1}{\sqrt{2\pi}} \frac{e^{-\frac{(t-t_0)^2}{2a^2}}}{a}$$

$$\int_{-\infty}^{\infty} \delta(t - t_0) dt = 1 .$$

where b is the average time of transit from X to Z. If the point of injection is "between" Z and X,

$$C_2(t) = C_1(t) - mb/V. \tag{8}$$

Equations (7) and (8) give the flow through and the volume of any part of a circulation. Thus, let I be injected into the right heart at the rate m. The concentration in the aorta is

$$C_{a_1} = C_{v_1} - mb/V + m/F, \tag{9}$$

where F is the cardiac output, b is the mean transit time from the right heart to the aorta, V is the blood volume, and C_v is the concentration of I in the superior and inferior venae cavae.

Let I be injected into an arm or leg vein; then

$$C_{a_2} = C_{v_2} - mb/V. \tag{10}$$

Equations (9) and (10) determine b and F for known V, which can be easily found from the final dilution of a known amount of a blood volume dye. The volume of the pulmonary circulation is

$$V_p = Fb\,. \tag{11}$$

Our interpretation of F will depend on our anatomical knowledge. Thus, if C_1 is for the internal carotid artery and C_2 is for the internal jugular vein, F is the flow through the internal carotid plus other inflow to the circle of Willis.

Since injection at a constant rate may not be experimentally feasible, more general methods of computation are necessary. These methods depend upon determining $f(t)$, which may be found from equation (4).

If for $t < 0$, $C_1(t) = 0$, equation (4) becomes

$$C_2(t) = \int_0^t C_1(t-\eta) f(\eta)\, d\eta\,. \tag{12}$$

Differentiation gives

$$C_2'(t) = C_1(0)\, f(t) + \int_0^t C_1'(t-\eta) f(\eta)\, d\eta. \tag{13}$$

Solving for $f(t)$, we have

$$f(t) = \frac{C_2'(t)}{C_1(0)} - \frac{1}{C_1(0)} \int_0^t C_1'(t-\eta) f(\eta)\, d\eta. \tag{14}$$

Successive substitution of the expression for $f(t)$ given by the right-hand side of equation (14) in $f(\eta)$, which occurs on the right-hand side, leads to a formal solution, namely, the series:

$$f(t)=\frac{C_2'(t)}{C_1(0)}-\frac{1}{C_1(0)}\int_0^t C_1'(t-\eta_1)C_2'(\eta_1)\,d\eta_1$$

$$-\sum_{m=2}^{m=\infty}\left(-\frac{1}{C_1(0)}\right)^{m+1}\int_0^t C_1'(t-\eta_1)\int_0^{\eta_1} C_1'(\eta_1-\eta_2) \tag{15}$$

$$\cdots\int_0^{\eta_{m-1}} C_1'(\eta_{m-1}-\eta_m)C_2'(\eta_m)\,d\eta_m\cdots d\eta_1 .$$

This series converges for all finite values of t, because $|C_1'(t)| \leqq P$ and $|C_2'(t)| \leqq Q$, where P and Q are positive numbers. Hence,

$$f(t)\leqq\frac{Q}{C_1(0)}\left[1+\frac{Pt}{C_1(0)}\cdots\frac{1}{n!}\left(\frac{Pt}{C_1(0)}\right)^n+\cdots\right], \tag{16}$$

or

$$f(t)\leqq\frac{Q}{C_1(0)}\,e^{\frac{Pt}{C_1(0)}} .$$

As $t\to\infty$, a sufficient condition for convergence is that $|C_2'(t)| \leqq Q$ and that

$$\int_0^\infty |C_1'(t)|\,dt \leqq C_1(0).$$

If $C_1(0)=0$, equation (15) has no meaning. In that case, differentiation of equation (13) gives

$$C_2''(t)=C_1'(0)f(t)+\int_0^t C_1''(t-\eta)f(\eta)\,d\eta . \tag{17}$$

If $|C_1'(0)|>0$, this equation can be solved for $f(t)$ as above. The proof of convergence is similar.

A more elegant method of solution of equation (14) is by Laplace transforms (Churchill, 1944). It can be written as the general integral equation of the convolution type,

$$Y(t)=F(t)+\int_0^t G(t-\eta)Y(\eta)\,d\eta , \tag{18}$$

whose transform is

$$y(s)=f(s)+g(s)y(s) \tag{19}$$

or,

$$y(s)=\frac{f(s)}{1-g(s)}. \tag{20}$$

The inverse of equation (20) gives $Y(t)$, which corresponds to $f(t)$ of equation (14), as an explicit function.

Thus we obtain formulae for the computation of $f(t)$ which are independent of the method of injection, although concentrations following instantaneous injection should give a most rapidly convergent solution.

Once we know $f(t)$, we can easily correct concentration curves for recurrent indicator and find the mean transit time, flow, and volume for a part of the circulation. The only limitations of the method are the accuracy with which measurements of instantaneous concentration can be carried out and the degree to which circulation is altered as a result of experimental manipulation.

LITERATURE

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