Dynamics of T-1824 Distribution in Patients with Traumatic Arteriovenous Fistulas

By GEORGE E. SCHREINER, NORBERT FREINKEL, JOHN W. ATHENS, AND WILLIAM STONE

Wide acceptance has been given to the expansion of “blood volume” in the presence of an arteriovenous fistula. Most clinical measurements have been made with abbreviated technics of T-1824 dilution. In the present study, carried out on casualties of the Korean War, significant expansion of the “rapidly distributing T-1824 and effective circulating albumin” were found in 31 patients with traumatic arteriovenous fistulas. Analyses of dye disappearance slopes, prolonged studies with labeled albumin and dye infusion have been used to investigate the dynamics of these measured expansions.

INJECTED T-1824 rapidly and quantitatively forms a stable linkage with plasma albumin and thereafter distributes approximately through the total pool of exchangeable albumin.1 Thus, the immediate dilution of dye obtained by extrapolation of the 10 to 30 minute slope (the “rapidly distributing T-1824 space”) assumes physiologic significance independent of the controversial attempts to define its anatomic boundaries as a “plasma volume.”4 It can be viewed as a measurement of the virtual volume occupied by that fraction of the total albumin pool which partakes in the most rapid exchanges of protein.

Early migration of protein-bound dye is probably dependent upon cardiovascular dynamics of mixing, transepithelial filtration rates and accessibility of perivascular protein depots. Large arteriovenous fistulas in man may present deviations in all three mechanisms. Such patients have an elevated cardiac index, an enlarged central volume by the Newman calculation,6 acceleration of both “peak” and “manifest” recirculation times as measured from the T-1824 dye curve,4 renal retention of sodium,7 increased pulse pressure and heart rate8,11 and have been labeled hypervolemic on the basis of 10 minute T-1824 spaces.12 The present studies were therefore carried out in patients with arteriovenous fistulas in order to investigate: (1) the incidence of an increase in the “rapidly distributing T-1824 space,” (2) the dynamics of such an increase when it occurs, and (3) its possible dependence upon altered distribution and metabolism of plasma protein.

MATERIALS AND METHODS

The patients were servicemen wounded in Korea. Arteriovenous fistulas resulted from direct trauma to blood vessels by small bullets and shell fragments. Initial measurements were made from one to eight (mean: 2.8) months after wounding with the exception of two patients whose small fistulas recurred after one and three years respectively. Control subjects were comparably confined hospital patients and ambulatory investigators and laboratory personnel.

All subjects were fasting and had complete bedrest for at least 12 hours preceding the studies. After collection of undyed blood samples by gentle withdrawal from a number 18 gauge Cournand needle placed under procaine anesthesia in an antecubital vein, 12 to 25 mg. of T-1824 were injected into a contralateral vein. Injection standards were prepared by dilution of an identical amount of dye with distilled water to a total volume of 1000 ml. An aliquot of this solution was later mixed with the patient’s own blank plasma to rule out any non-linear effect of plasma color on dye color. The amount injected was thus determined colorimetrically for each patient. Samples were again collected without hemostasis at 10, 15, 20, 25, and 30 minutes and transferred to siliconed test tubes containing dry heparin and inverted against parafilm. Hematocrit tubes were prepared in triplicate and centrifuged at 2800 revolutions per minute (1650 g.) for 45 minutes. Samples for colorimetry were centrifuged at 2800 rpm for 15 minutes, separated by pipetting and centrifuged a second time. All samples were read at 610 millimicrons in a Coleman Junior Spectrophotometer set at 100 per cent transmittance.
with the patient's own blank plasma. The "rapidly
distributing T-1824 space" was defined as that
volume occupied by the proteins with which the
T-1824-albumin complex has exchanged at the com-
pletion of intravascular mixing. It was measured by
conventional dilution technics:

\[ V = \frac{I}{C_0} \]  

where \( V \) = the rapidly distributing T-1824 space
(ml.), \( I \) = the amount of T-1824 injected (mg.), and
\( C_0 \) = the theoretic concentration of T-1824 at zero
time as determined by semilogarithmic extrapola-
tion of dye disappearance during the first 30 min-
utes (mg./ml.).

Values so derived represent minimal volumes
since most potential extravascular components of
the rapidly distributing T-1824 space would have
concentrations of protein which are lower than those
observed in plasma.

The immediate distribution of T-1824 does not
differ from that of iodinated (I\(^{131}\)) albumin.\(^1\)\(^4\)\(^5\)
The dilution principle was, therefore, extended to
quantify "effective circulating albumin" on the
assumption that the observed ratio of dyed/undyed
albumin was constant throughout the rapidly ex-
changing portions of the total albumin pool. Total
proteins and albumin fractions were determined on
serum by the method of Reinhold.\(^1\)\(^6\)

The slope (\( k \)) of the disappearance of dye during
the interval between 10 and 30 minutes following
injection was derived from the early exponential
relationship:

\[ C_t = C_0 e^{-kt} \]  

where \( C_t \) = The concentration of T-1824 at time \( t \)
(e.g., mg. dye/ml. plasma at 30 minutes), and
\( t - t_0 = 30 \) minutes.

To facilitate comparison, all values of T-1824
space and protein are presented as milliliters or
grams per kilogram of body weight. Calculation of a
portion of the data according to surface area did
not seem to improve the scatter.

An attempt was made to compare relative rates
of protein turnover in normal subjects and in
patients with patent arteriovenous fistulas. Subjects
were given a single injection of the same lot of
I\(^{131}\) labeled human serum albumin.\(^*\) The "apparent
biologic half life" of albumin was determined by
graphic analysis of the exponential disappearance
of I\(^{131}\) from the plasma during the second to the tenth
day after injection.\(^†\) Technical details have been
previously published.\(^1\)\(^\dagger\)\(^10\)

\* Abbott Laboratories.

\† It is appreciated that half-life values so derived
need not reflect absolute rates of turnover; since the

**Results**

"Rapidly distributing T-1824 spaces" were
measured preoperatively in 31 patients with
arteriovenous fistulas, in 29 patients after sur-
gical removal of their fistulas and in 30 control
subjects. The 90 individual determinations and
mean values of early T-1824 distribution are
plotted in figure 1.

Effective circulating (albumin) was deter-
mined in 26 preoperative, 26 postoperative
and 19 control subjects. Mean values were
1.71, (s.d = .2) 1.51, (s.d = .2) and 1.50
(s.d = .2) Gm. per kilogram, respectively.

![Fig. 1. Plot showing early T-1824 distribution
compartments. S. D. (\( \sqrt{S/N} \)) of preoperative patients
was 5.5 cc, s.d. of the mean (S/\( \sqrt{N} \)) was .99. S. D.
(\( \sqrt{S/N} \)) of postoperative patients was 4.3 cc, s.d. of
mean (S/\( \sqrt{N} \)) was .80. S. D. (\( \sqrt{S/N} \)) of control sub-
jects was 4.2 cc, s.d. of mean was .77. Since levels
of plasma albumin in the three
groups were similar, the derived values for
effective circulating (albumin) exhibited
the same scatter. In all studies, the postoperative
and control groups were not significantly dif-
ferent. They were, therefore, merged for fur-
ther analysis. This combined group differed
significantly from the preoperative group in all
measurements. The probability of this differ-
ence occurring by chance was less than 1 in
1000. No correlation could be achieved by
sampling time was short, metabolic degradation of
albumin may not be a true first order reaction, and
there is no assurance that large molecules such as
albumin ever reach equilibrium throughout their
ultimate distribution compartment following a single
injection.
classifying the site of involvement. When the volume measurements were divided by 1 minus the hematocrit reading, the range of the fistula group became 65.8 to 108.5 ml per kilogram with a mean of 84 ml per kilogram as compared with a control mean of 71 ml per kilogram. Since mean hematocrit ratios were similar in the three groups, this calculation had little significance in the present study.

T-1824 spaces in the 19 individuals studied both before and after surgical closure are presented in figure 2. Sixteen patients demonstrated a greater than 5 per cent reduction from the preoperative T-1824 space. If the postoperatively measured amount of reduction is interpreted as being equivalent to the elevation produced by the presence of a fistula, then the per cent elevations ranged from 1 to 50 and averaged 16.7. The preoperative increase in circulating albumin averaged 18 per cent. In general, patients with the higher initial values had the greater reduction in T-1824 space and effective circulating albumin.

The rates of dye disappearance in 31 patients with open fistulas were found to vary greatly between individuals. The \( k \times 10^{-5} \) ranged from \(-35\) to \(-637\) and averaged \(-350\). The use of a single 10 minute dilution value instead of the extrapolated zero level in calculation of the "rapidly distributing T-1824 space" would therefore have resulted in a discrepancy ranging from \(+8\) to \(+190\) ml with an average of \(+108\) ml. Preoperative slopes, in general, were flatter than normal slopes. This was best seen when slopes of the same individual were compared pre- and postoperatively. Preoperative/postoperative slope ratios were less than unity in 15 out of 18 cases. The mean ratio was 0.775. Individual ratios are presented at the base of figure 2.

Late disappearance of I\(^{131}\)-labeled albumin was measured in five preoperative, four postoperative (early), and nine control subjects. Despite the limitation of this method, the turnover of albumin during the second to tenth day following administration was substantially shorter in the patients with arteriovenous fistulas. The apparent "biologic half-life" of I\(^{131}\)-labeled albumin averaged 6.1 (range: 5.1 to 7.8) days in the preoperative patients, 8.8 (range: 7.8 to 11.3) days in the postoperative patients and 9.5 (range: 8.3 to 10.6) days in the control subjects.

Three patients with arteriovenous fistulas were given priming injection of T-1824 and then infused with dye at a constant rate by means of a Bowman pump for from 360 to 385 minutes. One hour after reaching constant concentration of dye in the plasma, the infusion was stopped and the decremental slopes measured during the subsequent 180 to 210 minute period. Slopes obtained in this manner were less steep than those observed following a single injection of T-1824. The slopes \((k \times 10^{-5})\) were \(-17\), \(-41\), and \(-59\) respec-
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Slopes of early dye disappearance following a single injection of T-1824 were also obtained in these three patients before and after surgery and following the rapid administration of 1000 ml. of normal saline (A-V fistula closed). The characteristic relationships are seen in figure 3 which compares these slopes in a single individual. Acceleration of intravascular dynamics of mixing by an arteriovenous fistula or infusion of dye to near equilibrium uniformly diminished the subsequent rate of disappearance of T-1824 from the plasma.

DISCUSSION

In the present study, many patients with arteriovenous fistulas exhibited significant expansion of the "rapidly distributing T-1824 space." This expansion was correlated roughly with the size of the fistula and could be reversed by operative repair of the arteriovenous shunt. It may be pertinent to examine some of the implications of an enhanced early dilution of T-1824.

Following intravenous injection, T-1824 rapidly forms a stable linkage with circulating plasma albumin. Subsequent serial decreases in the concentration of dye within the plasma approximate the distribution curve characteristic of albumin. Thus, the dye-protein complex is mixed progressively through various subdivisions of a "total T-1824 space" which includes both intravascular and extravascular tributaries. During any finite period the apparent rate of removal of T-1824 from the plasma represents the difference between filtration and diffusion outwards from the circulation and "feed-back" inwards into the circulation. The latter process becomes increasingly manifest as mixing proceeds until eventually T-1824 has equilibrated throughout its ultimate compartment of distribution. Thereafter, the slowest rate of dye disappearance is obtained since loss is uncomplicated by mixing phenomena and is governed predominantly by metabolic degradation. Theoretically, demonstration of such a "metabolic slope" can be attempted either (1) by allowing a single injection of label to diffuse to equilibrium and measuring the plasma disappearance over many days thereafter (the empiric and currently used two to three-day period has not been clearly proven to accomplish this objective), or (2) by infusing from a pump at a constant rate until well after the rate of infusion equals the rate of disappearance of label from its equilibrated compartment.

Intravascular mixing is complete within 10 minutes following administration of T-1824. It has been suggested that disproportionate exchange with perivascular proteins1-5 may occur during this period although lack of homogeneous blood samples prevents documentation of early mixing phenomena. Conceivably, initial rapid mixing within a larger portion of "the total T-1824 space" could modify the subsequent rate of dye disappearance. The slope measured after initial mixing (for example, the conventional 10 minute to 30 minute slope) would then be more shallow since it would be taken out of a later, and therefore flatter, segment of the curve of progressive distribution.

Obviously many other factors besides mixing may contribute to the configuration of disappearance slopes. Nonetheless, in 15 out of 18 patients used as their own controls, the preoperative rate of disappearance of T-1824 during the first 30 minutes was less rapid than its postoperative counterpart. This could mean either: (1) a significantly diminished rate of metabolic degradation (a flatter "ultimate slope"), (2) initial (10 minutes) mixing in a larger fraction of the ultimate distribution compartment, or (3) a genuine expansion of "plasma volume" accompanied by reduced exchange with extravascular sites. The first possibility was tested by observing the "turn-over" of 131I-labeled human serum albumin during a 10-day period. In five preoperative patients, the late rates of disappearance were more rapid than normal. Indeed, even some early postoperative patients seemed to share this phenomenon. The strikingly altered hemodynamics associated with an arteriovenous fistula would make either of the other two explanations more probable. The methods used in the present study cannot distinguish between the latter two possibilities. It is not unlikely that both may be operative. Although such a
distinction has basic importance such a separation may not be conceptually important. If albumin bound dyes can rapidly equilibrate in a larger space in subjects with arteriovenous fistulas, then other substances bound to plasma protein or protein itself can do likewise.

The phenomenon may have physiologic significance independent of the controversial attempts to assign anatomic boundaries to “the rapidly distributing T-1824 space.” Epstein, Post, and MacDowell have shown that patients with arteriovenous fistulas manifest renal retention of sodium. This would presumably result in an expanded extracellular fluid but need not make such fluid available to the circulation. In the presence of an arteriovenous fistula, the accessibility of a larger space for rapid distribution of albumin may well be one of the actual mechanisms for increasing the “effective” circulating volume even above and beyond the increase in physically intravascular volume.

SUMMARY

1. Significant expansions of the rapidly distributing T-1824 compartment were found in 31 patients with traumatic arteriovenous fistulas as compared with the values measured in 29 postoperative and 30 control subjects. Differences between pre- and postoperative measurements were most consistent when the postoperative patient was used as his own control.

2. In 15 of 18 patients the preoperative disappearance slope of T-1824 during the first 30 minutes was less steep than its postoperative counterpart. Preoperative/postoperative slope ratios, late “metabolic slopes,” and slopes of dye disappearance after prolonged infusion have been used to investigate the dynamics of these measured expansions in early dilution of T-1824.

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