The Measurement of Liver Circulation by Means of the Colloid Disappearance Rate

I. Liver Blood Flow in Normal Young Men

By Ernest L. Dobson, Ph.D., George F. Warner, M.D., Caroline R. Finney, A.B., and Muriel E. Johnston, M.A.

A method for calculating the liver blood flow by means of the rate of disappearance of colloidal chromic phosphate from the blood has been reviewed. This method has been applied to the study of liver circulation in a group of 29 fasting normal men. The significance of the colloid disappearance rate constant as a physiologic expression of the liver blood flow has been discussed and the average value obtained for this constant in normal young men was \(0.287 \pm 0.007\) min. Extra hepatic colloid localization, hepatic efficiency for colloid removal, speed of mixing, and type and time of sampling have been discussed.

Until recently the measurement of the circulation of blood through the liver in humans has been hampered by technical difficulty. The impetus given by the advent of intravascular catheterization has aided the problem of liver circulation measurement, and this technique in conjunction with bromsulfalein and urea excretion has been utilized extensively by Bradley and coworkers,1, 2 by Myers,3 and by Sherlock and associates.4

Simplification of the measurement of liver circulation is afforded by a method developed in this laboratory by which the rate of disappearance of colloid is determined.

Method

A complete discussion of this method has been given elsewhere by Dobson and Jones.5 Briefly, however, the method consists of measuring the removal rate of colloid particulate matter from the blood stream by the phagocytes of the liver and spleen. In the present study, the disappearance rate of colloidal chromic phosphate labelled with the radioisotope \(P^{32}\) was measured in a group of fasting, normal young men. Following the intravenous injection of 5.0 ml. of colloidal chromic phosphate containing 2 to 4 microcuries* of \(P^{32}\), 5.0 ml. serial blood samples (arterial, venous, or both) were taken at frequent intervals. Simultaneous blood volume measurements were made by adding 17 mg. of the blue dye T-1824 to the injection. After collection of the samples, the \(P^{32}\) activity of 2.0 ml. aliquots of whole blood was determined with a Geiger-Müller counter. The T-1824 concentration was determined spectrophotometrically in the plasma of the remaining 3.0 ml. of the samples.

Calculations

The colloid concentration of the samples is measured by the incorporated \(P^{32}\) activity. When this is plotted on semilogarithmic paper as a function of time, a curve is obtained whose initial portion, following a rapid rise due to mixing, is straight. The duration of the straight portion varies between 5 and 10 minutes (fig. 1). This initial portion of the multicomponent exponential curve closely approximates

* The amount of radioactivity injected is well within the safe tracer dose range. Four microcuries of \(P^{32}\) distributed in a liver of average size will give an initial dose rate of 0.1 r per day and a total cumulative dose of 2 roentgens. The radiation received from the fluoroscopy during a hepatic catheterization is of the order of 10 times greater than that received from the labelled chromic phosphate.

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a simple exponential which may be represented by the equation $C = C_0 e^{-kt}$ where $C$ is the concentration at any time $t$, $C_0$ is the initial concentration and $k$ is a constant. The slope of this straight line represents the fraction of the total blood volume perfusing the liver per unit time, and has been termed the colloid disappearance-rate constant, identical with splenohepatic localizations in other species, that is, dog, rabbit, mouse, and chicken, have been found to be quite low, amounting to about 10 per cent.\textsuperscript{5, 6}

2. Efficiency of Removal. It is assumed that the colloid particulate matter is removed by the liver and spleen with a high degree of efficiency in a single passage. This has been shown to be true in the mammalian species mentioned above. The method of preparation of the colloid results in a heterogeneous mixture of particle sizes. Very small particles, amounting to about 0.5 per cent of the total $P^{32}$ activity injected, have been shown to be responsible for the tail portion of the disappearance curve which follows the initial straight line portion (fig. 1). Although the liver is highly efficient in removing large particles, it presumably is poorly efficient in removing these very small particles. The over-all efficiency is probably about 90 per cent.\textsuperscript{5}

Assumptions

The use of this method for the accurate determination of liver blood flow involves four important assumptions:

1. Specific Localization. It is assumed in normal humans that the injected colloidal material localized specifically in the reticuloendothelial cells of the liver and spleen. Since the liver and spleen are in series with each other, relative distribution between these two organs does not affect the calculations.\textsuperscript{5} Extra
3. Use of Initial Straight Portion of the Curve. Although the complete curve has been shown to be a multicomponent exponential one,1 disregarding the slower components and simply using the initial slope produces only a small error. This is true because of the small contribution made by these slower components produced by the small-sized particles.

4. Mixing. The correct interpretation of the colloid disappearance curve as a measure of liver circulation requires that mixing of the injected material within the circulating blood volume be essentially complete before samples are used for such measurement. Mixing times have been determined from the simultaneous use of T-1824 with the chromic phosphate injection. Early points before mixing is complete are then disregarded when the disappearance slope is determined. Dye levels which have risen to within 10 per cent of the final equilibrium value indicate that the label has mixed with 90 per cent of the circulating blood. This extent of mixing was accepted as complete. Although this criterion of mixing was usually reached in two minutes (fig. 1), a few of the mixing times were prolonged to between 5

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Average ........................................ 2.50 ± 0.07* 0.282 ± 0.008 2.44 ± 0.06 0.287 ± 0.007 8.5

* All errors are expressed as standard error of the mean.
and 10 minutes. Greatly prolonged mixing times may introduce serious difficulty in determining the initial slope.

An attempt has been made to correct for mixing influences by expressing the sample data as a ratio of chromic phosphate concentration to T-1824 concentration. When points are plotted using this ratio, a curve is obtained in which the rapid rise due to mixing is eliminated (fig. 2). The general features of this ratio curve are: (1) an initial horizontal portion which represents a lag period between the time of injection and the time of arrival at the sampling site of labelled blood which has perfused the liver; and (2) a logarithmic slope which is equivalent to the straight portion of the plain chromic phosphate disappearance curve previously described (fig. 1).

**Results**

Chromic phosphate disappearance curves and simultaneous T-1824 mixing curves have been obtained in 29 normal, fasting young men. Venous subjects were obtained in all, and in five subjects simultaneous arterial samples were taken. The data from venous sampling are presented in table 1. The values for the disappearance slope have been expressed both as half-time and as \( k \), where \( k = \frac{1}{t_{1/2}} \). The blood volume as measured with T-1824 is expressed both as liters and as per cent of the body weight.

**Discussion**

The average value for \( k \) derived from the disappearance of chromic phosphate from venous blood is \( 0.282 \pm 0.008 \) minute\(^{-1}\). When mixing influences are corrected for by the use of the ratio CrPO\(_4\)/T-1824, the average value for \( k \) is \( 0.287 \pm 0.007 \) minute\(^{-1}\). From the close agreement between these two values it appears that mixing errors are minimal in the normal individual. However, in patients with deficient mixing the use of the dye or some other agent as an indicator of mixing is imperative.

From the data in table 1, the liver blood flow in liters per minute can be calculated. Thus with a blood volume corresponding to 8.5 per cent of his body weight, a 75 Kg. man would have 6.4 liters of blood. Of this volume, 28.7 per cent or 1.8 liters will pass through the liver per minute. The average value for the blood volume obtained from measurements of labeled red blood cells summarized by Berlin and Lawrence\(^7\) is 6.9 per cent of the body weight. This value may be preferable to the T-1824 value; when this value is used rather than the 8.5 per cent obtained from the T-1824 dye measurements in our study, the liver blood flow in the example cited becomes 1.5 liters per minute. This agrees almost exactly with liver blood flow values obtained by others using different methods.\(^1\)\(^-\)\(^4\)

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<th>Venous Curve k(min(^{-1}))</th>
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The disappearance rate constant, \( k \), which represents the fraction of the blood volume perfusing the liver per minute appears to be a very satisfactory method for expressing the liver blood flow. It avoids the discrepancies which have been observed in the various methods of blood volume measurement. It has more physiologic significance than the simple quantitative flow expressed in liters per minute because it reflects the extent of equilibration between the liver and the other body tissues. As far as the metabolic interrelation between the liver and the other body tissues is concerned the colloid disappearance-rate constant may be of even greater significance than the blood-tissue perfusion factor.

A similar constant for the rate of removal of
bromsulfalein is discussed by Ingelfinger and co-workers. They term their constant “percentage disappearance rate” (P.D.R.). Its average value is considerably smaller than the average value for k obtained with chro mic phosphate because of the relative inefficiency of the liver for the removal of bromsulfalein as compared with chromic phosphate. The inefficiency of the extraction of bromsulfalein in a single passage precludes the use of this single injection method for the calculation of liver blood flow.

Repeated measurements of liver blood flow in the same individual employing chromic phosphate have been found to agree, indicating no difficulty with the saturation effects proposed by Ingelfinger and co-workers in their studies with bromsulfalein.

A comparison of the values of k obtained from simultaneous arterial and venous data in five individuals is shown in table 2. The difference between the average k values obtained from arterial and venous curves is small, amounting to only 10 per cent. This difference becomes even smaller, less than 2 per cent, when the arterial and venous ratio curves are compared. This data implies that venous sampling is adequate for obtaining the disappearance constant, k, in normal individuals.

The ratio (CrPO4/T-1824) curves as already shown in figure 2 present an initial horizontal portion. The duration of this lag probably represents the summation of the arm-to-arm circulation time and the time of splanchnic transit. The slope following the initial lag represents the rate of disappearance of colloid from the labeled blood pool, which is constantly expanding during the mixing period, and consequently might be expected to show a changing slope. The magnitude of this change should be a function of the relative magnitudes of the cardiac output and the circulating blood volume. The data obtained in this study do not uniformly show a changing slope possibly because in the normal individuals investigated, differences between the magnitude of cardiac output and circulating blood volume were not sufficiently great. Furthermore, any minor differences that may have existed would tend to be obscured by rapid mixing.

**Summary**

1. A method for calculating the liver blood flow by means of the rate of disappearance of colloidal chromic phosphate from the blood has been reviewed.

2. This method has been applied to the study of liver circulation in a group of 29 fasting normal men.

3. The significance of the colloid disappearance-rate constant as a physiologic expression of the liver blood flow has been discussed.

4. The average value obtained for k in the normal group studied was 0.287 ± 0.007 minute⁻¹. Depending upon the value accepted for the blood volume this will give a liver blood flow of from 1.5 to 1.8 liters per minute.

5. Extrahepatic colloid localization, hepatic efficiency for colloid removal, speed of mixing, and type and time of sampling have been discussed.

**SUMARIO ESPAÑOL**

Un método para calcular la circulación hepática por medio de la velocidad de desaparición de fósforo crómico coloidal de la sangre se describe. Este método se ha aplicado al estudio de la circulación hepática en un grupo de 29 sujetos normales en ayunas. El significado del constante de velocidad de desaparición del coloide como una expresión fisiológica de la circulación hepática se discute y el valor promedio obtenido para esta constante en sujetos jóvenes normales fue 0.287 ± 0.007 min⁻¹. Se discute la localización extrahepática del coloide, la eficiencia hepática para remover el coloide, la velocidad de mezcla y el tipo e intervalo de la toma de muestras.

**REFERENCES**


3. **Myers, J. D.**: The hepatic blood flow and splanchnic oxygen consumption of man. Their estimation from urea production or bromsulphalein...


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