

Blood Disappearance Rates of Colloidal ¹⁹⁸Au in Normal and Cirrhotic Subjects: A Control and Clinical Study

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＝국문초록＝

교양 ¹⁹⁸금의 혈중제거율 : 그 정상치의 결정과 肝경변증에서의 동태

가톨릭의과대학 방사선과

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정맥에 주사된 膠樣 방사성물질은 肝에 있는 Kupffer 세포가 가진 탐식작용에 의해서 혈류로부터 거의 완전히 제거된다.

이 원리는 正常人과 肝경변증환자에서 肝혈류량을 측정하는데 이용된다. 일반적으로 肝경변증때에는 肝에서의 교양물질 추출율이 저하되기 때문에 혈중에서의 제거가 늦어진다하며, Shaldon 등은 혈중제거율측정을 이용하여, 추출율의 저하가 肝內에서 생기는 동맥과 정맥간의 단락(短絡) 때문에 초래되는 것을 증명하였다.

최근 혈중제거율을 몇가지 肝질환을 진단하는데 이용한 보고가 나왔다. 그러나 그 방법에 대한 상세한 검토가 없었던 것 같다.

저자는 이번 연구에서 손쉽게 얻을 수 있는 교양¹⁹⁸금을 사용하여 교양물질의 혈중제거율 측정방법을 검토하여 이 검사가 임상에서 通常적으로 쓰일 수 있음을 밝혔다.

① 정상인과 환자가 섞인 52명을 대상으로 동일인에서 24~48시간 간격을 두고 반복측정한 혈중제거율치의 오차는 통계학적으로 무시할 수 있었으며, 따라서 이측정은 근소한 오차한계내에서 되풀이할 수 있는 것을 알았다.

② 정상인 172명에서 얻은 측정치를 토대로 하여 혈중제거율 정상치가 3.31 ± 0.73 분임을 알았다(교양금 입자의 크기에 따라 이 측정치는 달라진다).

③ 조직검사로 진단이 확정된 肝경변증환자 23명을 조사하여 91.3%에서 혈중제거율이 정상한계를 넘어 延長되는 것을 알았다.

결론으로 혈중제거율검사는 임상에서 손쉽게 실시할 수 있는 肝기능검사가 될 수 있다고 생각되며, 특히 肝경변증을 진단하는데 도움이 된다고 믿는다.

That intravenously injected radioactive colloidal particulates are very effectively eliminated from the blood stream by Kupffer cells of the liver¹⁾ has been successfully adopted to the measurement of the hepatic blood flow in normal and cirrhotic subjects by Vetter, Falkner and Neumayr,²⁾ Vetter et al.,³⁾ Halpern et al.⁴⁾ and Benacerraf et al.⁵⁾ These early workers have

noted a significant reduction in the hepatic blood flow in the cirrhotics.

Rankin, Playoust and Beal⁶⁾ in 1961 assessed the significance of alterations in the efficiency of hepatic extraction of ³²P-labelled chromic phosphate in patients with various liver diseases and have found that a decrease in the extraction rate is related to the severity of hepatic dysfunction.

tion. They have also observed that in liver cirrhosis, extrahepatic uptake of radioactive colloidal particulates becomes conspicuous in the bone marrow. Employing a disappearance-rate method, Shaldon et al.⁷⁾ have disclosed that a reduction in hepatic extraction efficiency in cirrhosis is due to intrahepatic arteriovenous shunt of blood flow which then bypasses Kupffer cells in "internal Eck fistulae."

Recently, Taplin et al.⁸⁾ used the disappearance rates of colloidal radiogold and radioiodinated rose bengal for the differential diagnosis of various hepatobiliary diseases. Also in a paper on the scan findings in liver cirrhosis, Christie et al.⁹⁾ made a note on disappearance rates of colloidal ¹⁹⁸Au with one figure which illustrated a semi-quantitative relation between the "clearance curves" and the severity of cirrhosis.

Review of the literature, however, failed to reveal previous publications concerning the detail aspects of clinical application of this simple yet valuable method of evaluating the liver from functional standpoint.

The present investigation has been undertaken to evaluate the validity of blood disappearance-rate measurements and their applicability to the diagnosis of liver cirrhosis.

MATERIALS AND METHOD

The blood disappearance rate was measured in the following manner. A straight-bore collimator was placed over the ear with the patient lying in the right lateral recumbent position on a scan table and 1.5 μ c per 10 kg of body weight of radiogold* suspended in 2 ml of normal saline or 5 per cent dextrose solution was injected rapidly into the antecubital vein. The impulse of disappearing activity was fed into a recorder (Nuclear Chicago Model R1000A) through an analy-

tical count-rate meter (Nuclear Chicago Model 1620 C) and the half time ($T_{1/2}$) was calculated from the recorded paper according to the method used by Taplin et al.⁸⁾, (Fig. 1). The examination requires no preparation and can be carried out on an ambulatory basis.

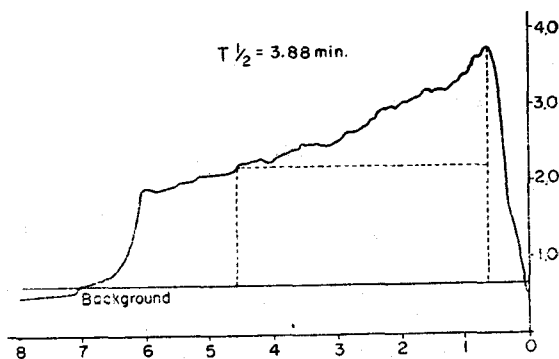


Fig. 1. A typical disappearance-curve of radioactivity from the peripheral blood as determined by over-ear counting. The $T_{1/2}$ value is calculated by a simple geometrical drawing.

RESULTS

Validity and Reproducibility of Measurements

In order to test both validity and reproducibility of the method and measurements, paired observations were made in 52 consecutive patients.

The disappearance-rate study was duplicated in each patient at an interval of 24 or 48 hours. The results obtained were shown in Table 1. Of 52 paired data, those of 2 cases with abnormally great differences (Cases 27 and 40) between the initial and second studies were discarded following rejection test¹⁰⁾ according to the formula:

$$r_o = \frac{d_{\max} - \bar{d}}{s}$$

where d_{\max} is the maximum difference, \bar{d} the mean, and s the standard deviation.

The differences of remaining pairs were treated statistically according to the formula:

* Obtained from Commissariat à l'Énergie Atomique, France. Average size of particles is 300 Å and specific activity is more than 30 mC/ml.

$$|t| = \frac{|\bar{d}-0|}{s/\sqrt{N}} \quad (11)$$

Where \bar{d} is the mean of difference, s the standard deviation, and N the number of samples.

From this, it was found that the differences were not significant statistically indicating that the method and measurements are valid and reproducible within a negligible range of errors.

Normal Controls

One-hundred-and-seventy-two apparently normal subjects of both sexes, with ages ranging from 18 to 47 years, were studied as a control at the St. Mary's Hospital, Catholic Medical College, Seoul, Korea. These subjects were all without detectable abnormality by both physical and laboratory examinations including conventional liver function tests. The subjects with the past history of either jaundice, liver diseases, other significant ailments or of habitual consumption of alcohol were not included.

The $T_{1/2}$ values obtained from this control group ranged from 1.75 to 4.84 minutes with mean being 3.31 ± 0.73 (Fig. 2). It follows, therefore, that the upper tolerance limits of normal values with 95-per-cent inclusion of items at 95-per-cent confidence level is 4.89 minutes.¹¹⁾

Incidentally, it is shown that lowering of the specific activity of colloidal ¹⁹⁸Au due to natural decay does not influence disappearance-rate determinations at least within the period of our experience.

Table 1. Paired observations in 52 consecutive patients ($T_{1/2}$ in minutes)

Case No	Initial measurements	Secend Measurements	Difference of measurements
1	3.36	3.15	0.21
2	2.42	3.00	-0.58
3	4.10	4.84	-0.74
4	2.84	3.52	-0.68
5	3.26	3.00	0.26

6	3.31	2.68	0.63
7	2.31	2.36	-0.05
8	4.57	4.63	-0.06
9	4.47	4.47	0
10	4.10	3.52	0.58
11	3.47	3.00	0.47
12	6.84	6.00	0.84
13	2.42	3.52	-1.10
14	3.42	3.57	-0.15
15	2.89	3.68	-0.79
16	6.05	6.47	-0.42
17	6.68	7.36	-0.68
18	4.21	3.78	0.43
19	5.68	5.15	0.53
20	3.00	2.36	0.64
21	7.89	8.05	-0.16
22	6.10	6.52	-0.42
23	4.73	4.78	-0.05
24	3.42	4.00	-0.58
25	8.10	8.15	-0.05
26	6.31	6.42	-0.11
27	5.94	3.68	2.26
28	6.05	5.80	0.25
29	3.75	3.42	0.33
30	3.15	3.10	0.05
31	3.10	3.42	-0.32
32	10<	10<	0
33	3.04	3.00	0.04
34	3.78	3.15	0.63
35	10<	10<	0
36	3.57	4.00	0.43
37	3.57	2.63	0.94
38	4.36	4.90	-0.54
39	5.53	5.26	0.27
40	6.52	1.63	4.89
41	3.90	3.37	0.53
42	3.82	3.10	0.72
43	3.52	3.26	0.26
44	3.27	3.00	0.27
45	6.36	6.40	-0.04
46	3.40	2.36	1.04
47	3.31	3.47	-0.16
48	5.40	4.90	0.50
49	4.20	4.38	-0.18
50	2.74	3.30	-0.56
51	4.80	4.20	0.60
52	3.32	3.26	0.06

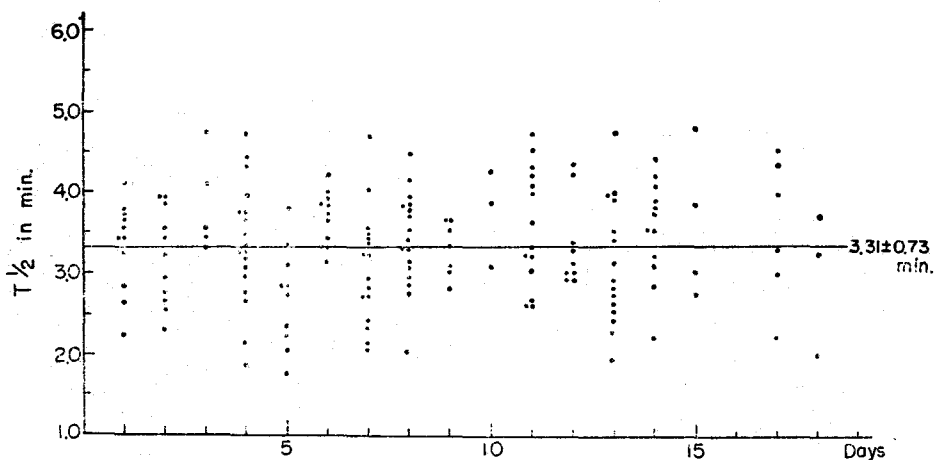


Fig. 2. Scattergram of the $T_{\frac{1}{2}}$ values obtained from 172 cases of apparently normal subjects studied at various intervals after arrival of radiopharmaceutical. Lowering of specific activity due to natural decay seems not influential on the determinations of disappearance rates.

CLINICAL OBSERVATION

A review of the pathological file covering the period of from January 1966 to December 1966 revealed 47 cases of proven diagnosis of liver cirrhosis. Of these, there were 23 patients in whom the disappearance-rate measurements were available.

In all but 2 cases (91.3 per cent) the disappearance rates were significantly delayed with the $T_{\frac{1}{2}}$ values not being in the range of normal which was set by the aforementioned control study of 172 normal subjects. The histological findings in the 2 cases was "periportal fibrosis of mild degree" and the $T_{\frac{1}{2}}$ value was 3.6 and 4.3 minutes, respectively.

COMMENT

Since the original study of Vetter, Falkner and Neumayr²⁾ in 1954, the blood disappearance rate has been widely used in the measurements of the hepatic blood flow both in normal and abnormal conditions from without. Regarding the hepatic blood flow in the cirrhotic patients a consensus among many investigators^{4, 5, 6)} is that there is a significant reduction in blood flow. It is apparent, therefore, that there would be a delay in

the disappearance rate of colloidal particulates from the blood stream in the cirrhotic patients since the disappearance is intimately related to the amount of blood flow through the sinusoids of the liver where the particulated materials are phagocytized by Kupffer cells.

Another characteristic feature of the cirrhotic liver has been disclosed by the ingenious work of Shaldon et al.⁷⁾ These workers have used a disappearance-rate method in studying hemodynamics in the cirrhotic livers and have found that a reduction in hepatic extraction of colloidal particulates is due to the development of arterio-venous shunts within the cirrhotic liver. Through such shunts the blood bypasses Kupffer cells resulting in an escape of the particulates from extraction, and thus in prolonged circulation in the peripheral blood stream.

The present study showed significant delay in disappearance rates in the great majority of the patients with liver cirrhosis (91.3 per cent) substantiating the anticipation.

Although there are some complicated factors involved in the measurements of disappearance rates such as the size and uniformity of colloidal particulates,^{3, 6)} the method is a valuable adjunct in evaluating the liver function especially in

terms of hemodynamics. Finally, it is felt that like other liver function tests the disappearance-rate measurements should preferably be interpreted in context with clinical findings.

CONCLUSION AND SUMMARY

The measurement of disappearance rates of colloidal ¹⁹⁸Au from blood flow is an excellent index of hepatic blood flow and of extraction efficiency of Kupffer cells. This, therefore, can be used as an ancillary examination of liver function especially in the patients with altered hemodynamics of the liver and portal system as in liver cirrhosis.

The examination is very simple and can be performed without preparation of patients on an ambulatory basis. Normal values of disappearance rates were set by a control study of 172 normal subjects. Validity and reproducibility of the measurements were assessed.

Increment in the amount of colloidal ¹⁹⁸Au to be injected as made necessary by natural decay did not seem to affect the determinations of disappearance rates.

The disappearance rates were found to be significantly delayed in the patients with liver cirrhosis.

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REFERENCES

- 1) Dobson, E. L. and Jones, H. B.: *The Behavior of Intravenously Injected Particulate Material: Its Rate of Disappearance from the Blood Stream as a Measure of Liver Blood Flow.* *Acta Med. Scandinav.* 144. Suppl. 273, 1952.
- 2) Vetter, H., Falkner, R., and Neumayr, A.: *The Disappearance Rate of Colloidal Radiogold from the Circulation and Its Application to the Estimation of Liver Blood Flow in Normal and Cirrhotic Subjects.* *J. Clin. Invest.* 33:1594, 1954.
- 3) Vetter, H., Grabner, G., Hoffer, R., Neumayr, A. and Prazer, O.: *Comparison of Liver Blood Flow Values Estimated by the Bromsulphalein and by the Radiogold Method.* *J. Clin. Invest.* 35:825, 1956.
- 4) Halpern, B. N., Biozzi, G., Benacerraf, B., Stiffel, C. and Hillenmand, B.: *Cinetique de la phagocytose d'une serumalbumine humaine specialement traitee et radiomarquee, et son application a l'etude de la circulation hepatique chez l'homme.* *C. R. Soc. Biol.* 150: 1307, (Paris), 1956.
- 5) Benacerraf, B., Biozzi, G., Halpern, B. N., Stiffel, C., and Mouton, D.: *Phagocytosis of Heat-Denatured Human Serum Albumin Labelled with ¹³¹I and Its Use as a Means of Investigating Liver Blood Flow.* *Brit. J. Exp. Path.* 38:35, 1957.
- 6) Rankin, J. G., Playoust, M. R. and Beal, R. W.: *Significance of Alterations in Extraction and Distribution of Colloidal Chromic Phosphate in Patients with Liver Diseases.* *J. Lab. & Clin. Med.* 58:920, 1961.
- 7) Shaldon, S., Chiandussi, L., Guevara, L., Caesar, J., and Sherlock, S.: *The Estimation of Hepatic Blood Flow and Intrahepatic Shunted Blood Flow by Colloidal Heat-Denatured Human Serum Albumin Labeled with ¹³¹I.* *J. Clin. Invest.* 40 :1346, 1963.
- 8) Taplin, G. V., Hayashi, J., Johnson, D. E. and Dove, E.: *Liver Blood Flow and Cellular Function in Hepatobiliary Diseases. Tracer Studies with Radiogold and Rose Bengal.* *J. Nucl. Med.* 2:204, 1961.
- 9) Christie, J. H., Macntyre, W. J., Crespo, G. G. and Koch-Weser, D.: *Radioisotope Scanning in Hepatic Cirrhosis.* *Radiology* 81:455, 1963.
- 10) Grubbs, F. E.: *Sample Criteria for Testing Outlying observations.* *Am. Math. Statistics.* 21:27, 1950.
- 11) Dixon, W. J. and Massey, F. J.: *Introduction to Statistical Analysis.* p.124. 2nd ed., New York. McGraw-Hill Book Comp. Inc., 1957.