Title
THE MEASUREMENT OF LIVER CIRCULATION BY MEANS OF THE COLLOID DISAPPEARANCE RATE. II. CHANGES IN LIVER BLOOD FLOW PRODUCED BY CHRONIC LYMPHATIC CEUKEMIA

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THE MEASUREMENT OF LIVER CIRCULATION BY MEANS OF THE COLLOID DISAPPEARANCE RATE. II.
CHANGES IN LIVER BLOOD FLOW PRODUCED BY FEEDING, EPINEPHRINE ADMINISTRATION, AND CHRONIC LYMPHATIC LEUKEMIA*

George F. Warner, Ernest L. Dobson, Muriel E. Johnston
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ABSTRACT

Human liver blood flow has been measured by the colloid disappearance rate method in one pathological and in two experimental conditions. The eating of a light meal always produced an increase in blood flow, while the administration of epinephrine produced quite variable results. The degree but not the direction of this variability was proportional to the dose of epinephrine. Increased splanchnic blood flow was observed in chronic lymphatic leukemia, and was correlated with spleen size.

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INTRODUCTION

A description of the method for calculating the liver blood flow by
means of the rate of disappearance of colloidal chromic phosphate from the
blood, and the application of this method to the study of liver circulation in
fasting normal men has been previously described. This paper is concerned
with the changes in the colloid disappearance rate produced by certain ex-
perimental and pathologic factors.

METHOD

A complete discussion of the calculations and the assumptions involved
in the interpretation of the colloid disappearance rate as a measure of liver
blood flow has been presented in a previous communication. Briefly, the
method consists of following the rate of removal from the blood of $P^{32}$-
labelled colloidal chromic phosphate by the phagocytes of the liver and spleen.

Following the intravenous injection of $P^{32}$-labelled chromic phos-
phate, ** 5.0 ml serial venous blood samples were taken at frequent intervals
for 10 minutes. Simultaneous blood volume measurements were made in most
cases by adding 10-20 mgm. of the blue dye T-1824*** to the injection volume.
After collection of the samples, the $P^{32}$ activity was determined with a Geiger-
Muller counter, and the T-1824 concentration in the plasma was determined
spectrophotometrically. The ratio CrP04/T-1824 of the samples was then
plotted on semi-logarithmic paper as a function of time. The plot thus obtained

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search under Contract N70nr-295/4.

** The dosage was 2-4 microcuries in the normal individuals, a safe tracer
dose. However, some of the patients with leukemia received larger amounts,
usually because of a high background of activity from radiophosphorus
therapy.

***The T-1824 was obtained from the Warner Chilcott Co., New York.
is straight during the disappearance of 90% of the injected dose, and can be described as a simple exponential 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 the semi-log plot 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 $k$ in the equation above. The disappearance rate constant is related to the half-time of disappearance by the expression, $k = \frac{0.693}{t_{1/2}}$. The liver blood flow in liters per minute may be obtained by multiplying the blood volume by $k$. The ratio $CrP04/T-1824$ is used in an attempt to correct the early points for mixing influences.

RESULTS

Changes in Liver Blood Flow Produced by Feeding

All subjects were fasted overnight and a base-line liver blood flow and blood volume determination was made the following morning. A light meal consisting of 1-2 sandwiches, milk, and cake was then eaten by the subject and repeat determinations of liver blood flow and blood volume were made approximately one hour after the meal. The effect of such feeding on liver blood flow in six normal individuals is shown in Table 1. As a result of the meal the colloid disappearance rate constant, $k$, shows an increase of approximately 40% over the pre-prandial fasting value. This represents an average increase in liver blood flow of 650 cc./min. The blood volume showed no change as a result of the meal.

Changes in Liver Blood Flow Produced by the Administration of Epinephrine

All subjects were fasted overnight and a base-line determination of liver blood flow and blood volume was made. In eight normal males a moderately large dose of epinephrine (1.0 mgm. adrenalin chloride, Parke-Davis) was injected subcutaneously. In five other normal subjects a smaller dose of 0.25 mgm. was used. These data are summarized in Table 2. On the average, epinephrine appears to have little effect on liver blood flow. However, the data show marked differences in individual instances both in magnitude and direction when the larger dose was used, although there was a consistent increase in pulse pressure and pulse rate in all. The smaller dose of epinephrine produced a definite increase in pulse rate and a minor
increase in pulse pressure. Liver blood flow measurements after the smaller dosage showed the same erratic variations in direction as those noted with the larger dose but were of smaller magnitude. No significant change in blood volume was observed in any of the subjects.

When the absolute magnitude of the change (without regard to direction) after epinephrine is considered, a striking difference between the large and small doses is noted. The average percent change in liver blood flow after 1.0 mgm. epinephrine subcutaneously is 34, and after the smaller dose of 0.25 mgm. is 18. In four subjects on whom repeat measurements were made soon after the subcutaneous injection of 0.25 cc. normal saline, and after the application of heat to the abdomen, the average percent change was less than two.

Changes in Liver Blood Flow in Chronic Lymphatic Leukemia

Chromic phosphate disappearance rate determinations were made on eight male patients with well-established chronic lymphatic leukemia. Table 3 shows the essential clinical data together with the results of 13 liver blood flow and blood volume measurements on the eight patients. The average half-time of disappearance of colloidal chromic phosphate, without regard to clinical status or therapy, is 1.4 min. \( k = 0.496 \). This increase in rate of disappearance implies an increase in liver blood flow of 73% over the flow in young normal males.\(^1\) Liver blood flow determinations in a limited number of normal males in older age groups show no marked alterations from the value obtained in the young normal group. In a separate study seven normal men with ages ranging from 38-59 years showed an average disappearance half-time of 2.4 min.

The data in Table 3 also show a positive correlation between the size of the spleen, the degree of anemia, and the liver blood flow. These relationships are further emphasized by successive measurements on the same individuals. These patients (HEN, PAL, BRE, TRU) showed varying degrees of change in their anemia and splenomegaly. In one patient (PAL), values before and after splenectomy show a reduction in the increased liver blood flow after convalescence from the surgical procedure.
DISCUSSION

Changes in Liver Blood Flow After Feeding

An increase in splanchnic blood flow after eating has long been suspected. The common sensation of drowsiness following a heavy meal presumes a decrease in cerebral blood flow occasioned by increased demand in the splanchnic area. Lewis has concluded from BSP clearance studies that there is such an increased splanchnic blood flow in rabbits, and the present study demonstrates a similar consistent increase in human liver blood flow following a light meal.

Changes in Liver Blood Flow Produced by Epinephrine

Liver blood flow changes with adrenalin have been observed in many animals ranging from frogs to monkeys and man. A wide varietiy of methods, both direct and indirect, have been employed, and the results of these investigations are conflicting and confusing. Burton-Opitz, using mechanical stromuhrs in dogs showed that intrahepatic artery or intra-portal vein injections of adrenalin reduced the flow in these vessels. Deysach showed a differential effect of intra-portal vein injections of adrenalin on the flow through the perfused excised surviving livers of rabbits, cats and monkeys. Small doses caused marked increases and large doses decreases in flow. However, it should be noted that the flow rates cited are considerably lower than those subsequently recorded by others in intact animals. Burton-Opitz also observed that systematic adrenalin increased the hepatic artery flow in the dog if there was a rise in systemic blood pressure. Grayson and Johnson, on the other hand, report that in the rabbit if the blood pressure is maintained constant by use of a reservoir, the infusion of adrenalin produces a sustained diminution in hepatic blood flow. More recently Bearn, Billing and Sherlock, and Bradley and coworkers, using BSP and hepatic catheterization techniques, have reported marked increases in blood flow through the human liver using intravenous and intramuscular doses of adrenalin without an accompanying rise in mean arterial blood pressure.

The results of the present study are somewhat at variance with the reports just cited in that they do not reflect the consistent increase in liver blood flow described by them. A decrease in disappearance rate noted in some of the subjects could be explained by a change in the removal efficiency induced by adrenalin. A reduction in removal efficiency could be caused either by a reduced phagocytic activity of the Kupffer cells or by the opening
of arterio-venous shunts providing a bypass of blood away from the phagocytic cells. Reduction in phagocytosis by either of these two mechanisms of sufficient extent to cause an apparent reduction in liver blood flow to one-half (subjects NEE, STE) is unlikely. In the present study the subcutaneous route of administration was used, whereas Bearn et al used the intravenous route and Bradley and associates the intramuscular route. Variability in the rate of absorption from subcutaneous epinephrine injection may occur as a result of local vasoconstrictor action. For this reason measurements were deferred until a definite systematic effect was noted. In all subjects given 1 mgm. epinephrine a consistent increase in pulse rate and pulse pressure was obtained before the liver blood flow measurement was made.

The complexity and multiplicity of the possible sites of action of epinephrine as regards the entire splanchnic vascular bed, the overall effect on the systemic blood pressure, and the presence of varying amounts of nor-epinephrine in USP Epinephrine, may well combine to produce a variable and unpredictable response in a given individual and result in the variations noted in this study.

Changes in Liver Blood Flow in Chronic Lymphatic Leukemia

There are two principal explanations for the increased colloid disappearance rate seen in chronic lymphatic leukemia. One of these is the possibility of increased extra-spleno-hepatic removal, and the other an actual increase in splanchnic blood flow.

Animal experiments indicate that the bone marrow removes only 0.5-5.0 percent of intravenously injected colloidal material. The bone marrow hyperplasia which accompanies leukemia might be expected to cause an increase in extra-spleno-hepatic removal. However, for bone marrow hyperplasia to account for the increased removal rate seen in leukemia, it would have to increase in activity from 30 to 300 times above normal. Although tissue distribution data in chronic lymphatic leukemia is not available, the marked increase in colloid disappearance rate observed in these patients can be explained more reasonably as a result of an increase in liver blood flow rather than as a result of hyperactivity of the phagocytic elements of the bone marrow.

Due to the already high phagocytic efficiency of the normal liver (85 percent), the increased removal rate of colloidal chromic phosphate seen in chronic lymphatic leukemia cannot be accounted for by a simple increase in the phagocytic elements of the spleno-hepatic system which might result from
splenomegaly. Thus if the efficiency were to increase to 100 percent, the removal rate could be increased by only 15 percent. The increased size of the spleen, however, may directly account for increased splanchnic circulation by increasing the volume contribution of the splenic stream to the portal flow.

The clinical data indicate a positive correlation between the increased colloid removal rate and the increase in spleen size. This is most likely due to a direct increase in blood flow through the enlarged spleen. However, several indirect mechanisms may also be operating to produce the increased blood flow through the liver. Among these would be a possible generalized increase in circulation (cardiac output) resulting from the accompanying anemia and the increased metabolic rate frequently present in these patients.

**SUMMARY AND CONCLUSIONS**

1. Liver blood flow increases following a light meal.
2. Liver blood flow changes are variable after epinephrine administration, and the degree of variability is related to the dose.
3. A marked increase in colloid disappearance rate is seen in patients with chronic lymphatic leukemia. This change is due to increased splanchnic blood flow rather than to changes in phagocytic efficiency.
REFERENCES


4. ______________, The vascularity of the liver. X. The influence of adrenaline upon the venous inflow. Quart. J. Exper. Physiol. 5, 329 (1912).


TABLE 1

The Effect of Feeding on the Colloid Disappearance Rate Constant, k, and on the Estimated Hepatic Blood Flow (EHBF)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age yrs.</th>
<th>Liters</th>
<th>% Body wt.</th>
<th>( \frac{1}{2} ) min.</th>
<th>k ( \text{min}^{-1} )</th>
<th>EHBF liters ( \text{per min} )</th>
<th>( \frac{1}{2} ) min.</th>
<th>k ( \text{min}^{-1} )</th>
<th>EHBF liters ( \text{per min} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCH</td>
<td>22</td>
<td>6.3</td>
<td>6.3</td>
<td>2.6</td>
<td>0.27</td>
<td>1.70</td>
<td>1.6</td>
<td>0.43</td>
<td>2.71</td>
</tr>
<tr>
<td>ELD</td>
<td>21</td>
<td>6.5</td>
<td>8.5</td>
<td>2.2</td>
<td>0.31</td>
<td>2.01</td>
<td>1.8</td>
<td>0.39</td>
<td>2.54</td>
</tr>
<tr>
<td>HER</td>
<td>21</td>
<td>6.2</td>
<td>7.1</td>
<td>2.4</td>
<td>0.29</td>
<td>1.80</td>
<td>1.8</td>
<td>0.39</td>
<td>2.42</td>
</tr>
<tr>
<td>SAN</td>
<td>23</td>
<td>6.2</td>
<td>8.4</td>
<td>2.4</td>
<td>0.29</td>
<td>1.80</td>
<td>1.4</td>
<td>0.50</td>
<td>3.10</td>
</tr>
<tr>
<td>JON</td>
<td>25</td>
<td>7.7</td>
<td>11.0</td>
<td>2.5</td>
<td>0.28</td>
<td>2.16</td>
<td>2.3</td>
<td>0.30</td>
<td>2.31</td>
</tr>
<tr>
<td>DEA</td>
<td>22</td>
<td>4.5</td>
<td>7.7</td>
<td>2.7</td>
<td>0.26</td>
<td>1.17</td>
<td>2.2</td>
<td>0.32</td>
<td>1.44</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td>8.2</td>
<td></td>
<td>±0.08**</td>
<td>±0.008</td>
<td>1.77</td>
<td>±0.16</td>
<td>±0.048</td>
<td>2.42</td>
</tr>
</tbody>
</table>

* Plotted as the ratio \( \frac{\text{CrPO}_4}{T1824} \)

**All errors expressed as standard error of the mean using \( \sigma_m = \sqrt{\frac{\Sigma d^2}{N-1}} \).
TABLE 2
The Effect of Large and Small Doses of Subcutaneous Epinephrine on the Colloid Disappearance Rate Constant, k, and the Associated Effect on Blood Pressure and Pulse Rate

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age yrs.</th>
<th>$t_2$ min.</th>
<th>k min. $^{-1}$</th>
<th>Blood pressure</th>
<th>Pulse rate</th>
<th>Pre-epinephrine, 1.0 mgm</th>
<th>k min. $^{-1}$</th>
<th>Blood pressure</th>
<th>Pulse rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEE</td>
<td>23</td>
<td>2.2</td>
<td>0.32</td>
<td>120/80</td>
<td>80</td>
<td>4.2</td>
<td>0.16</td>
<td>170/65</td>
<td>104</td>
</tr>
<tr>
<td>STE</td>
<td>23</td>
<td>2.2</td>
<td>0.32</td>
<td>---</td>
<td>--</td>
<td>4.0</td>
<td>0.17</td>
<td>---</td>
<td>--</td>
</tr>
<tr>
<td>MER</td>
<td>22</td>
<td>2.8</td>
<td>0.25</td>
<td>110/60</td>
<td>72</td>
<td>3.2</td>
<td>0.22</td>
<td>160/70</td>
<td>104</td>
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<tr>
<td>LIS</td>
<td>21</td>
<td>3.4</td>
<td>0.20</td>
<td>118/75</td>
<td>60</td>
<td>2.2</td>
<td>0.32</td>
<td>150/60</td>
<td>100</td>
</tr>
<tr>
<td>SAN</td>
<td>23</td>
<td>2.6</td>
<td>0.27</td>
<td>115/75</td>
<td>80</td>
<td>3.1</td>
<td>0.22</td>
<td>140/55</td>
<td>100</td>
</tr>
<tr>
<td>PAC</td>
<td>22</td>
<td>2.6</td>
<td>0.27</td>
<td>100/70</td>
<td>64</td>
<td>3.0</td>
<td>0.23</td>
<td>125/55</td>
<td>76</td>
</tr>
<tr>
<td>JOH</td>
<td>22</td>
<td>2.4</td>
<td>0.29</td>
<td>110/75</td>
<td>68</td>
<td>2.4</td>
<td>0.29</td>
<td>180/60</td>
<td>72</td>
</tr>
<tr>
<td>SChr</td>
<td>21</td>
<td>2.8</td>
<td>0.25</td>
<td>105/75</td>
<td>80</td>
<td>2.4</td>
<td>0.29</td>
<td>115/75</td>
<td>88</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td>2.6</td>
<td>0.27</td>
<td></td>
<td></td>
<td>3.1</td>
<td>0.24</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age yrs.</th>
<th>$t_2$ min.</th>
<th>k min. $^{-1}$</th>
<th>Blood pressure</th>
<th>Pulse rate</th>
<th>Post-epinephrine, 0.25 mgm</th>
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</thead>
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<tr>
<td>DUL</td>
<td>23</td>
<td>2.2</td>
<td>0.32</td>
<td>110/70</td>
<td>64</td>
<td>2.4</td>
</tr>
<tr>
<td>CAR</td>
<td>21</td>
<td>2.4</td>
<td>0.29</td>
<td>100/65</td>
<td>52</td>
<td>2.7</td>
</tr>
<tr>
<td>KAP</td>
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<td>2.4</td>
<td>0.29</td>
<td>125/70</td>
<td>68</td>
<td>1.8</td>
</tr>
<tr>
<td>MEL</td>
<td>23</td>
<td>2.0</td>
<td>0.35</td>
<td>100/60</td>
<td>68</td>
<td>2.4</td>
</tr>
<tr>
<td>LAM</td>
<td>21</td>
<td>2.6</td>
<td>0.27</td>
<td>125/80</td>
<td>72</td>
<td>2.0</td>
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<tr>
<td>Average</td>
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<td>2.3</td>
<td>0.30</td>
<td></td>
<td></td>
<td>2.3</td>
</tr>
</tbody>
</table>

*All errors expressed as standard error of the mean using $\sigma_m = \sqrt{\frac{\Sigma d^2}{N-1}}$. 
### TABLE 3

The Effect of Chronic Lymphatic Leukemia on the Colloid Disappearance Rate Constant, k, and on the Estimated Hepatic Blood Flow (EHBF)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age yrs.</th>
<th>Weight kgm.</th>
<th>T-1824 Blood Volume liters</th>
<th>$t_{1/2}$ min.</th>
<th>k 1/min.</th>
<th>EHBF l/min.</th>
<th>Spleen size cms.*</th>
<th>Hgb gms.</th>
<th>RBC millions</th>
<th>WBC (% lymphs)</th>
<th>date of measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEN</td>
<td>67</td>
<td>81.0</td>
<td>5.5</td>
<td>2.0</td>
<td>0.35</td>
<td>1.92</td>
<td></td>
<td>4</td>
<td>11.6</td>
<td>3.4</td>
<td>90,000 (90)</td>
</tr>
<tr>
<td>HEN</td>
<td>71</td>
<td>77.0</td>
<td>8.5</td>
<td>1.7</td>
<td>0.41</td>
<td>3.48</td>
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<td>10</td>
<td>8.5</td>
<td>2.3</td>
<td>80,000 (98)</td>
</tr>
<tr>
<td>AND</td>
<td>61</td>
<td>75.9</td>
<td>6.3</td>
<td>1.0</td>
<td>0.69</td>
<td>4.35</td>
<td></td>
<td>7</td>
<td>9.4</td>
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<td>13,000 (81)</td>
</tr>
<tr>
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<td>1.1</td>
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<td>5</td>
<td>7.1</td>
<td>2.8</td>
<td>3,300 (36)</td>
</tr>
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<td></td>
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<td>12.6</td>
<td>4.0</td>
<td>23,000 (81)</td>
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<td>80.5</td>
<td>6.5</td>
<td>1.3</td>
<td>0.53</td>
<td>3.44</td>
<td></td>
<td>5</td>
<td>10.2</td>
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<td>66,000 (50)</td>
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<td>BRE</td>
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<td>80.5</td>
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<td>1.4</td>
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<td>9.5</td>
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<td>4.69</td>
<td></td>
<td>7</td>
<td>11.7</td>
<td>3.5</td>
<td>12,000 (69)</td>
</tr>
<tr>
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<td>67.5</td>
<td>---</td>
<td>1.3</td>
<td>0.53</td>
<td>---</td>
<td>details not available</td>
<td>---</td>
<td></td>
<td></td>
<td>---</td>
</tr>
<tr>
<td>TRU</td>
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<td>6.2</td>
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<td>12</td>
<td>11.5</td>
<td>3.6</td>
<td>11,000 (83)</td>
</tr>
<tr>
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<td>66</td>
<td>69.8</td>
<td>6.1</td>
<td>2.2</td>
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<td>1.95</td>
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<td>6</td>
<td>14.0</td>
<td>4.7</td>
<td>5,200 (36)</td>
</tr>
<tr>
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<td>67</td>
<td>66.8</td>
<td>6.7</td>
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<td>12</td>
<td>12.1</td>
<td>4.4</td>
<td>9,400 (72)</td>
</tr>
</tbody>
</table>

*Centimeters below left costal margin at mid-clavicular line.