Hepatic Hemodynamics During Viral Hepatitis in Man

By Rudolf Preisig, M.D., James G. Rankin, M.B., M.R.A.C.P., Joseph Sweeting, M.D., and Stanley E. Bradley, M.D.

ALTERATIONS in hepatic hemodynamics might well play an important role in producing many of the effects of acute viral hepatitis in man. The architectural distortion secondary to ballooning of the parenchymal cells, tissue necrosis, active regeneration, and infiltration by masses of inflammatory cells undoubtedly interfere with perfusion of the sinusoids. According to Himsworth,¹ the resulting ischemia may actually produce additional injury primarily affecting the centrilobular cells. It is possible, also, that sinusoidal obstruction contributes to the pathogenesis of hepatomegaly by causing intrahepatic portal venous engorgement. Certainly splenomegaly and a moderate elevation in portal venous pressure—often in association with the appearance of esophageal varices—have been observed in patients shortly after the onset of viral hepatitis.² ³ The rapid decrease in liver size and increase in hepatic uptake of sulfobromophthalein sodium (BSP) during recovery is also in keeping with improvement in circulation at this time that might result both in better venous drainage and more effective delivery of dye to the cells.

Unfortunately, histological changes do not reliably characterize local circulatory patterns because preparatory manipulation results in loss of tissue fluids and collapse of vessels making it impossible to measure vascular cross-sections and volume directly. And, in addition, determination of hepatic blood flow during hepatitis by different methods has yielded conflicting results.² ⁴ ⁵ An attempt to resolve these difficulties is reported in this paper. The findings indicate that hepatic blood flow remains within normal limits, as Reichman and Davis⁶ have also reported. Portal hypertension appears to be attributable to obstruction of the portal venules with negligible effect upon the total resistance to blood flow. Intrahepatic vascular engorgement does not seem to contribute significantly to the hepatomegaly of hepatitis, since circulating splanchnic blood volume tends to decrease rather than rise. Inflammatory compression of the structures in the portal tracts could account not only for these results but also for evidence⁶ that biliary obstruction is a regular feature of viral hepatitis.

Methods

Fifteen patients ranging in age from 17 to 55 years who had been admitted to the Presbyterian Hospital with a diagnosis of viral hepatitis on the basis of typical clinical and biochemical changes were studied. Confirmatory liver biopsy was obtained in 12 within 48 hours of the initial studies to be described below. Serum hepatitis was suspected in three. Splanchnic hemodynamic measurements were made in 14, within 2 to 4 days following admission to the Presbyterian Hospital (on the average 19 days after clinical onset of hepatitis). These studies were repeated in two patients during “recovery” 14 and 21 days after initial study and in two at a time of complete clinical and biochemical “cure” 147 and 132 days after the first study. In one patient measurement was made once only during recovery.

All subjects were studied following an overnight fast and premedication consisting of saturated potassium iodide (500 mg per day for 2 days). At the time of study all were afebrile and comfortable, without evidence of distress, resting quietly on an air-cushioned fluoroscopy table.

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Catheterization of a right hepatic vein was performed under fluoroscopic control, using a no. 8 Cournand or Lehman catheter. On eight occasions, the catheter was thrust deeply into a right hepatic vein in order to measure wedged hepatic venous pressure (WHVP) by means of a Statham gauge and Sanborn recording apparatus (zero reference plane 4 cm posterior to the xyphoid process). For blood sampling the catheter tip was maintained at a position in the middle of the right lobe to avoid both obstruction to flow and the possibility of retrograde sampling. An indwelling polyethylene catheter (Deseret no. 17), placed in a vein of the opposite arm, served as the infusion site. Arterial blood samples were taken from a femoral artery using an indwelling polyethylene catheter, which had been inserted percutaneously by means of the Seldinger technique.

Indocyanine green* (ICG) was made up for infusion in a 0.6 g% solution of human serum albumin (Cutter) in normal saline. Such an infusion was shown to be stable for at least 1 week. After a priming dose of 15 mg ICG, the dye was infused intravenously at a constant rate (Bowman pump) of approximately 0.01 mg per minute per kilogram of body weight. Samples of arterial and hepatic venous blood were obtained alternately at 5-minute intervals after a 30-minute period of equilibration. The blood samples were immediately spun for 15 minutes at 2,350 rpm, and plasma optical density of each was determined (Beckman DU-810 mμ) at constant room temperature and timed intervals after sampling with correction for plasma “blank.” Concentrations were read from a standard calibration curve prepared from known solutions of the dye made up in pooled human serum. Human serum was also used to dilute aliquots of the infusion (taken before and after each study as a check on stability) for determination of the concentration of ICG in the infusion mixture. Estimated hepatic blood flow (EHBF) was computed as in sulfobromophthalein method.  

Approximately 15 μc of colloidal denatured human albumin labeled with radioactive iodine (CA131I)* were administered as a single intravenous injection for the estimation of hepatic blood flow on 12 occasions during the ICG equilibration periods. Samples of hepatic venous blood (4 ml) were obtained at 3, 4, 5, 6, 8, 10, 20, 25, and 30 minutes after injection. To compensate for hepatic catheter delay time, samples of arterial blood were collected simultaneously by means of an identical catheter attached to the femoral arterial sampling site. The radioactivity of the 1-ml samples of plasma was measured in an automatic well-type scintillation counter (Nuclear-Chicago) before and after precipitation of protein to obtain values of protein-bound 131I (counts per minute per milliliter) for use in plotting the disappearance of CA131I from the blood and determination of the rate constant (k) of the initial “fast component curve.” Since CA131I within the splanchic vasculature is in effect “removed” from the total blood volume, the volume of distribution to which k relates may be taken as the extrasplanchnic blood volume or the difference between the total (TBV) and splanchic (SBV) blood volumes. The product of k and (TBV − SBV) is the hepatic clearance of CA131I which, when corrected for hepatic CA131I extraction (Ee) is equal to the hepatic blood flow (designated CAFB in this paper to distinguish it from EHBF measured by ICG). In determining Ee, when concentration changes so rapidly, it is important to allow for the time required for blood to perfuse the liver and to compare a given arterial blood sample with the hepatic venous blood derived from it. Since mean splanchic circulation time (MCT) was determined in the measurement of SBV by the regional dilution technique, it was possible to do this in the present study. Computation of CAFB was made; therefore, as:

$$\text{CAFB} = \frac{k \times (\text{TBV} - \text{SBV})}{\text{Ee}}$$

Splanchnic blood volume was measured by the regional dilution technique and MCT was calculated from the values for SBV and EHBF. Total blood volume was computed from the value for arterial plasma radioactivity 10 minutes following intravenous administration of a carefully measured quantity of RISA after the determination of SBV with correction for blank plasma radioactivity. The activity of the arterial plasma was compared with that of an aliquot of the injectate diluted in a known volume with addition of sufficient pooled human plasma to prevent adsorption of the tracer to glass.

Serum bilirubin concentration, serum alkaline phosphatase, glutamic oxaloacetic and glutamic pyruvic transaminase activities, cephalin-cholesterol flocculation, and thymol turbidity were measured by standard methods. The oxygen content of arterial and hepatic venous samples was measured by the manometric method of Van Slyke and Neill. Hepatic photoscans were made with a Magnascan (Picker) apparatus after intravenous administration of approximately 0.1 mc of 188Au.

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### Table 1

#### Results of Liver Function Tests in Acute Viral Hepatitis

<table>
<thead>
<tr>
<th>Name</th>
<th>Age, yr</th>
<th>Sex</th>
<th>Wt, kg</th>
<th>Time after onset, days</th>
<th>Serum bilirubin mg%</th>
<th>Serum alk. phosph., K.-AU*</th>
<th>SGOT, KU†</th>
<th>SGPT, KU†</th>
<th>Cephalin flocculation</th>
<th>Thymol turbidity</th>
<th>Plasma albumin, g</th>
<th>Protein γ-globulin, g%</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.P.</td>
<td>27</td>
<td>M</td>
<td>73</td>
<td>9</td>
<td>32.0</td>
<td>16</td>
<td>2300</td>
<td>1000</td>
<td>+</td>
<td>+</td>
<td>3.5</td>
<td>1.3</td>
</tr>
<tr>
<td>S.V.</td>
<td>23</td>
<td>M</td>
<td>73</td>
<td>12</td>
<td>15.2</td>
<td>17</td>
<td>410</td>
<td>390</td>
<td>0</td>
<td>0</td>
<td>4.1</td>
<td>1.1</td>
</tr>
<tr>
<td>R.B.</td>
<td>32</td>
<td>M</td>
<td>68</td>
<td>20</td>
<td>13.2</td>
<td>25</td>
<td>850</td>
<td>240</td>
<td>±</td>
<td>2‡</td>
<td>4.4</td>
<td>0.6</td>
</tr>
<tr>
<td>J.F.</td>
<td>36</td>
<td>M</td>
<td>73</td>
<td>23</td>
<td>12.0</td>
<td>28</td>
<td>520</td>
<td>320</td>
<td>3+</td>
<td>3+</td>
<td>4.1</td>
<td>1.6</td>
</tr>
<tr>
<td>S.S.</td>
<td>28</td>
<td>M</td>
<td>73</td>
<td>10</td>
<td>11.6</td>
<td>23</td>
<td>600</td>
<td>900</td>
<td>3+</td>
<td>3+</td>
<td>4.4</td>
<td>1.7</td>
</tr>
<tr>
<td>C.R.</td>
<td>25</td>
<td>F</td>
<td>59</td>
<td>13</td>
<td>7.4</td>
<td>16</td>
<td>1000</td>
<td>390</td>
<td>0</td>
<td>2+</td>
<td>3.8</td>
<td>1.7</td>
</tr>
<tr>
<td>B.D.§</td>
<td>17</td>
<td>M</td>
<td>57</td>
<td>24</td>
<td>6.0</td>
<td>22</td>
<td>250</td>
<td>400</td>
<td>±</td>
<td>2+</td>
<td>3.6</td>
<td>2.1</td>
</tr>
<tr>
<td>C.G.</td>
<td>18</td>
<td>M</td>
<td>66</td>
<td>19</td>
<td>4.8</td>
<td>12</td>
<td>110</td>
<td>200</td>
<td>3+</td>
<td>3+</td>
<td>4.0</td>
<td>1.9</td>
</tr>
<tr>
<td>M.P.</td>
<td>52</td>
<td>F</td>
<td>62</td>
<td>20</td>
<td>4.0</td>
<td>8</td>
<td>78</td>
<td>80</td>
<td>3+</td>
<td>3+</td>
<td>3.9</td>
<td>1.8</td>
</tr>
<tr>
<td>M.R.§</td>
<td>21</td>
<td>M</td>
<td>62</td>
<td>33</td>
<td>3.6</td>
<td>22</td>
<td>360</td>
<td>630</td>
<td>0</td>
<td>+</td>
<td>4.5</td>
<td>1.2</td>
</tr>
<tr>
<td>F.C.</td>
<td>19</td>
<td>M</td>
<td>62</td>
<td>21</td>
<td>3.2</td>
<td>25</td>
<td>1040</td>
<td>1200</td>
<td>3+</td>
<td>3+</td>
<td>4.5</td>
<td>2.2</td>
</tr>
<tr>
<td>A.V.</td>
<td>32</td>
<td>F</td>
<td>58</td>
<td>21</td>
<td>2.7</td>
<td>26</td>
<td>230</td>
<td>440</td>
<td>2+</td>
<td>3+</td>
<td>4.8</td>
<td>2.0</td>
</tr>
<tr>
<td>L.P.</td>
<td>24</td>
<td>M</td>
<td>79</td>
<td>18</td>
<td>2.4</td>
<td>30</td>
<td>95</td>
<td>175</td>
<td>2+</td>
<td>0</td>
<td>4.5</td>
<td>1.0</td>
</tr>
<tr>
<td>T.G.</td>
<td>33</td>
<td>M</td>
<td>71</td>
<td>10</td>
<td>2.4</td>
<td>30</td>
<td>76</td>
<td>190</td>
<td>2+</td>
<td>4+</td>
<td>3.5</td>
<td>1.6</td>
</tr>
<tr>
<td>J.G.§</td>
<td>55</td>
<td>M</td>
<td>87</td>
<td>32</td>
<td>2.5</td>
<td>17</td>
<td>190</td>
<td>360</td>
<td>1+</td>
<td>3+</td>
<td>3.2</td>
<td>2.0</td>
</tr>
</tbody>
</table>

*Normal values: 0.6 ± 0.3 6 ± 2 18 ± 9 16 ± 8 0

*King-Armstrong units.
†Karmen units.
*Serum protein electrophoresis.
§Probable serum hepatitis.
**Results**

Although selection of patients to exclude those who were febrile, confused, and unable to understand the nature of the studies, or distressed by nausea, vomiting, diarrhea, or discomfort of any kind might have been expected to eliminate the more seriously ill and to minimize variability, the data summarized in table 1 attest, nevertheless, to considerable diversity among the patients who were the subjects of this study. All presented clinical findings consistent with the diagnosis of viral hepatitis, but it is evident that the severity of the disease and, presumably therefore, also the character of the expected hemodynamic adjustments under study varied widely. In table 1 the results of the usual liver function tests, arranged in order of decreasing hyperbilirubinemia, fail to show any clear-cut pattern of dysfunction that might be correlated with the degree of jaundice. Of particular importance from the standpoint of evaluating hepatic circulatory parameters was the observation that liver size and tenderness also failed to evince any overall correlation with the serum bilirubin concentration at the onset (that is, all except J.G. who was studied only once, during "recovery," about 32 days after onset). In four subjects (J.P., R.B., J.F., and C.R.) studied a second time during recovery or after complete "cure," bilirubinemia decreased in association with a decrease or disappearance of hepatomegaly and of other functional abnormalities in conformity with the usual clinical experience. These seeming inconsistencies may have arisen in part because the serum bilirubin concentration is affected by factors other than the severity of tissue injury, such as hemolysis, and in part because viral hepatitis affects both parenchymal cells and biliary tract tissues to a variable degree. In view of the clinical variability it was somewhat surprising to find a relatively uniform hepatic circulatory pattern.

**Hepatic Blood Flow**

Nearly every measurement of hepatic blood flow, regardless of the method of measurement and severity of hepatic injury, fell within normal limits (table 2). The values for EHBF (ICG) obtained in 14 patients during the acute phase of the disease (J.P. to T.G., table 2) ranged from 890 to 2,430 ml per min and averaged 1,510 ml per min (normal averaging 1,530 ± 300 ml per min by the BSP method). Of these, only two fell definitely outside the range defined by the normal average plus and minus two times the standard deviation (930 to 2,130 ml per min), viz. A.V. (890 ml per min) and C.G. (2,430 ml per min), the remainder tended to cluster about the mean. In two patients (J.P. and R.B.) studied again during recovery, EHBF changed very little (from 1,470 to 1,650 and from 2,190 to 1,920 ml per min, respectively). And in one man (J.C.) studied only during this phase, EHBF was 1,360 ml per min. EHBF was measured during the acute stage and again several months later after all clinical evidence of pathology had cleared in J.F. and C.R. It decreased from 1,890 to 1,710 ml per min in the former and from 1,470 to 980 ml per min in the latter.

It is of interest that the relatively larger fall in EHBF observed in C.R. was associated with a marked reduction in size of the liver. More data are needed to assess the possibility of a correlation between change in size of the liver and EHBF during the course of the disease with recuperation in individual patients. Certainly, in the data as a whole for all patients, there was no evidence of a correlation between size of the liver and EHBF. The observation that hepatomegaly was present in all without change in EHBF from normal is highly significant and implies, in fact, a relative reduction in hepatic blood flow per gram of tissue roughly proportional to the increment in mass.

On 12 occasions in 10 patients (in the acute phase, S.V., R.B., J.F., B.D., C.G., F.C., and T.G; in the recovery phase, J.P., R.B., and J.G., and after healing, J.F. and C.R.), hepatic blood flow was measured simultaneously as EHBF and CABF. With two exceptions (J.P. and S.V.), EHBF and CABF were in fairly
### Table 2

**Splanchnic Circulatory Measurements in Acute Viral Hepatitis**

<table>
<thead>
<tr>
<th>Name</th>
<th>Liver size/tender</th>
<th>Spleen size</th>
<th>ICG Method</th>
<th>CA¹³¹I Method</th>
<th>Hepatic oxygen A-V diff., vol %</th>
<th>Splanchnic MCT, sec</th>
<th>Spl., ml</th>
<th>Blood volume, Total ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.P.</td>
<td>4F/+</td>
<td>2F</td>
<td>P, mg% 0.43</td>
<td>159 28</td>
<td>1470</td>
<td>33.3</td>
<td>820</td>
<td>6180</td>
</tr>
<tr>
<td></td>
<td>3F/+</td>
<td>2F</td>
<td>C, ml 0.17</td>
<td>498 45</td>
<td>1650</td>
<td>1700 0.40 73</td>
<td>2710</td>
<td>33.9 930 5940</td>
</tr>
<tr>
<td>S.V.</td>
<td>2F/+</td>
<td>Ø</td>
<td>E, % 0.34</td>
<td>208 28</td>
<td>1270</td>
<td>590 0.25 57</td>
<td>1960</td>
<td>4.6 5090</td>
</tr>
<tr>
<td>R.B.</td>
<td>3F/+</td>
<td>1F</td>
<td>0.29 0.13</td>
<td>76 61</td>
<td>1920</td>
<td>2800 0.39 81</td>
<td>1820</td>
<td>3.2 43.0 5210</td>
</tr>
<tr>
<td>J.F.</td>
<td>RCM/+</td>
<td>Ø</td>
<td>0.33 0.20</td>
<td>652 70</td>
<td>1710</td>
<td>3700 0.31 74</td>
<td>2030</td>
<td>3.8 12.8 370 5380</td>
</tr>
<tr>
<td>S.S.</td>
<td>2F/+</td>
<td>1F</td>
<td>0.29 0.26</td>
<td>328 31</td>
<td>1470</td>
<td>8</td>
<td>52.1</td>
<td>1090 4260</td>
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<tr>
<td>C.R.</td>
<td>4F/+</td>
<td>Tip</td>
<td>0.17 0.10</td>
<td>434 76</td>
<td>980</td>
<td>3300 0.30 76</td>
<td>1180</td>
<td>6 24.1 400 4000</td>
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<tr>
<td>B.D.</td>
<td>2F/+</td>
<td>Ø</td>
<td>0.07 0.07</td>
<td>470 50</td>
<td>1560</td>
<td>1100 0.25 63</td>
<td>1570</td>
<td>10 35.5 930 4850</td>
</tr>
<tr>
<td>C.G.</td>
<td>RCM/0</td>
<td>Ø</td>
<td>0.23 0.27</td>
<td>320 25</td>
<td>2430</td>
<td>2050 0.35 59</td>
<td>2200</td>
<td>8 3.4 18.6 750 4500</td>
</tr>
<tr>
<td>M.P.</td>
<td>2F/0</td>
<td>2F</td>
<td>0.22 0.22</td>
<td>354 50</td>
<td>1190</td>
<td>9</td>
<td>4.2</td>
<td>10.5 210 3710</td>
</tr>
<tr>
<td>M.R.</td>
<td>2F/0</td>
<td>Tip</td>
<td>0.11 0.11</td>
<td>410 62</td>
<td>1110</td>
<td>2350 0.31 68</td>
<td>1280</td>
<td>12 32.3 590 3420</td>
</tr>
<tr>
<td>F.C.</td>
<td>1F/0</td>
<td>Ø</td>
<td>0.18 0.12</td>
<td>266 46</td>
<td>890</td>
<td>9</td>
<td>3.0</td>
<td>1.0 460 3700</td>
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<td>A.V.</td>
<td>2F/+</td>
<td>Ø</td>
<td>0.14 0.12</td>
<td>748 73</td>
<td>1710</td>
<td>0.38 63 1850 8.6</td>
<td>3.9</td>
<td>31.3 795 4290</td>
</tr>
<tr>
<td>L.P.</td>
<td>1F/0</td>
<td>Ø</td>
<td>0.14 0.12</td>
<td>530 54</td>
<td>1680</td>
<td>2300 0.32 69</td>
<td>1800</td>
<td>45.3 1260 5220</td>
</tr>
<tr>
<td>T.G.</td>
<td>RCM/+</td>
<td>Ø</td>
<td>0.07 0.07</td>
<td>157 18</td>
<td>1360</td>
<td>460 0.26 60</td>
<td>1380</td>
<td>12 25.1 570 6210</td>
</tr>
<tr>
<td>J.G.</td>
<td>3F/+</td>
<td>2F</td>
<td>0.37 0.38</td>
<td>1510 38</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: F = fingerbreadth; Ø = not palpable; RCM = at the right costal margin; ICG = indocyanine green; P = plasma ICG concentration; E = hepatic extraction of ICG; EHBFl = hepatic blood flow estimated by the ICG method; CA¹³¹I = heat denatured colloidal human serum albumin labeled with radioactive iodine; Pocts = plasma CA¹³¹I concentration at zero time by extrapolation; k = rate constant of CA¹³¹I disappearance from the plasma; Ec = hepatic extraction of CA¹³¹I; CABFl = hepatic blood flow estimated by CA¹³¹I method; WHVP = wedged hepatic venous pressure; MCT = mean circulation time; mean = average of values obtained only during the acute phases of the disease. All measurements made on the times indicated in table 1.
good agreement averaging 1,650 and 1,850 ml per min, respectively or 1,680 and 1,750 ml per min when J.P. and S.V. were excluded. CABF was followed sequentially in only two patients (R.B. and J.F.); in the first it decreased from 2,300 to 1,820 ml per min, and in the second, it changed very little, if at all, from 1,940 to 2,030 ml per min.

**Hepatic Extractions**

Since both methods agreed in indicating maintenance of hepatic blood flow within normal limits and since plasma concentrations were never excessively high (table 2), the reduction observed in the clearances of ICG and CA^{131}I must be ascribed entirely to impaired removal by the liver. The extraction of ICG (normally averaging 63\%^{10}) ranged from 21 to 73\% in the acute phase and was closely correlated (r = -0.522, \textit{P} < 0.05) with the bilirubin concentration. With recovery or healing the value returned to normal levels. In contrast, the extraction of CA^{131}I (normally about 95\%^{12}) was reduced almost as much, but failed to show any correlation with serum bilirubin concentration or to return to normal levels even several months after apparent healing (J.F. and C.R.). These changes in extraction of ICG and CA^{131}I could not be correlated either with the volume of blood flow or the mean splanchnic circulation time. Hence it must be concluded that they reflect changes in cellular function rather than in perfusion. Furthermore, no evidence of gross heterogeneity in the distribution of ^{198}Au was observed in "photoscans" obtained in eight patients during the acute phase of the disease.

Study of the hepatic oxygen extraction failed to throw light upon the character of perfusion or the tissue change. In the five patients in whom arterial-hepatic venous oxygen difference (A - HVO\textsubscript{2}) was measured during the acute phase, the values ranged from 3.0 to 4.6 vol\% (table 2) closely about the normal mean (3.9 ± 0.76 vol\%^{16}). Total splanchnic oxygen uptake (EHBF \times A - HVO\textsubscript{2}) tended to be high; in three (S.V., R.B., and C.G.) well above the normal mean (90, 90, and 83 vol per min, respectively, in contrast to the normal value\textsuperscript{16} of 64.1 ± 16.8 vol per min). In R.B., A - HVO\textsubscript{2} and total splanchnic uptake decreased markedly (from 4.5 to 3.2 vol\% and from 99 to 61 vol per min) during recovery, whereas in J.F. they increased somewhat with healing (from 3.0 to 3.8 vol\% and from 57 to 65 vol per min).

It should be stressed that the A - HVO\textsubscript{2} reflects uptake of oxygen by the extrahepatic splanchnic viscera as well as the liver and that computation of total splanchnic oxygen consumption on the basis of the EHB\textsubscript{F} may be too low by the extent to which portosystemic collateral drainage is unaccounted for. Extrahepatic splanchnic oxygen consumption probably accounts for more than half the total uptake in the normal so that relatively large changes in intrinsic hepatic uptake might be minimized or even hidden altogether in these figures. The lack of change in A - HVO\textsubscript{2} despite the evident reduction in EHB\textsubscript{F} per unit liver mass suggests, but does not prove, therefore, that hepatomegaly did not involve a proportionate increase in hepatic oxygen utilization.

**Splanchnic Blood Volume and Wedged Hepatic Venous Pressure**

The circulating splanchnic blood volume measured in 10 patients during the acute phase (J.P., R.B., J.F., C.R., B.D., C.G., M.P., F.C., A.V., and T.G., table 2) and in one during recovery only (J.G.) ranged from 210 to 1,260 ml or from 6 to 25\% of the total blood volume as compared with normal figures\textsuperscript{17} of 1,023 ± 301 ml and 19.1 ± 3.8\%, respectively. All but two values (in C.R. and T.G.) fell below the normal mean. In two patients studied during recovery (J.P. and R.B.), SBV tended to rise and in two studied after "healing" (J.F. and C.R.) it fell markedly to values less than the normal mean by more than two times the standard deviation. In general, SBV followed the splanchnic mean circulation time which ranged from 10.5 to 52.1 seconds, averaged 31.3 seconds as compared with the normal mean of 39.9 ± 5.8 seconds, and fell below the normal mean in all but two patients (C.R. and T.G.).
There was no evidence of a correlation between MCT and EHBFP nor between SBV and liver size. The marked reduction both in SBV and MCT after complete recovery in J.F. and C.R. was particularly puzzling. There was no reason whatever for believing that hepatic fibrosis or persistent portosystemic shunts had developed or that hepatic dysfunction (other than continued depression of E_c) persisted in either of these two patients.

Wedged hepatic venous pressure was measured during the acute phase in 10 subjects (R.B., J.F., S.S., C.R., B.D., C.G., M.P., M.R., F.C., and A.V.), during recovery in two (R.B. and J.G.) and after "healing" in two (J.F. and C.R.). The value for WHVP (table 2) was 12 mm Hg in two (F.C. and J.G.) and at approximately normal levels in the remainder, averaging 8.6 mm Hg. From this observation it may be concluded that the postsinusoidal vascular resistance was not much affected, if at all, by the change in hepatic size and the tissue damage of hepatitis. The values are in keeping with the normal systemic cardiocirculatory parameters. Arterial pressure and peripheral venous pressure were within normal limits in all subjects as was total blood volume. It should be emphasized, however, that all measurements were made at rest in recumbency under circumstances that precluded detection or evaluation of possible defects in hemodynamic adjustment to stress.

**Discussion**

According to the findings of this study, acute viral hepatitis does not appear to interfere significantly with total hepatic perfusion. Since three entirely different methods for the measurement of hepatic blood flow have yielded similar results, technical error that would affect measurements in precisely the same way would be a most unlikely explanation for the phenomenon. Owing to a marked reduction in removal and extraction of sulfobromophthalein sodium (BSP) by the liver in most patients with hepatitis, the BSP method could not be used in this study with confidence. Both colloidal denatured human serum albumin labeled with radioiodine (CA^{131}I) and indocyanine green (ICG) were found to be taken up in the splanchnic bed with sufficient avidity even under these conditions, however, to maintain extraction at a level high enough to permit their use in the single injection (CABF) and constant infusion clearance-and-extraction (EHBFP) techniques, respectively. It seems likely that removal of ICG and CA^{131}I from the blood flowing through the splanchnic bed occurs preponderantly, if not exclusively, in the liver. To some extent, the hepatic injury does result in a relatively greater importance than normal of splenic reticuloendothelial cells as evident in demonstrable splenic uptake of colloidal gold in four of eight patients in whom "photocans" were obtained. Nevertheless, even under these conditions, comparison of hepatic and splenic densities indicated that no more than a small and relatively insignificant fraction of colloidal was taken up in the extrahepatic splanchnic vasculature. It may be concluded, therefore, that both methods measured the volume of blood flowing out of the hepatic veins. The good agreement with the data published by Reichman and Davis, who used a third method that depends on measurement of the radioactivity over the liver following injection of RISA into the spleen, indicates further that collateral venous drainage of the portal bed probably did not affect the figures significantly. Loss of RISA by collateral "escape" would have resulted in falsely high values for hepatic blood flow by the method of Reichman and Davis.

Since the rise of portal venous pressure^{2,3} without change in sinusoidal pressure or hepatic blood flow implies an increase in portal venular resistance, the hepatic structural changes of viral hepatitis seem to act in some manner selectively to impede portal venous outflow. Portal venous flow would not be much diminished by such an obstruction because the venular resistance normally makes up less than 2% of the total resistance to portal flow through the splanchnic bed.^{18} Hence, a two-fold increment sufficient to account for the reported rise in portal venous...
pressure would reduce portal flow by no more than 5%, or total hepatic venous outflow by approximately 2 to 3%, an amount too small to detect by the methods available. There is no reason to suppose that hepatic arterial inflow is altered in any way. The lesion responsible for this effect lies in all probability within the portal tracts, presumably a result of the inflammation that is evident in local infiltrates of mononuclear cells, eosinophils, plasma cells, and lymphocytes. Compression of the bile ducts as well as the venous channels within the portal tract would also account for the elevation in serum alkaline phosphatase activity and the persistent reduction in BSP transfer maximum that are characteristic of hepatitis.\textsuperscript{6} The bulk of the portal tract is composed of a tightly interwoven connective tissue supplied by a capillary network originating chiefly in the hepatic arterioles. Since these capillaries (unlike the hepatic sinusoids) are constructed like those elsewhere in the body (Dr. Hans Popper, personal communication), it is probable that they are similarly characterized by intraluminal pressures approximating 32 mm Hg at the arteriolar end and dropping to 15 mm Hg at the venous end.\textsuperscript{19} With increased capillary permeability, blood pressures of this magnitude could readily produce a tense edema of the portal tracts with interstitial fluid pressures well in excess of those usually prevailing within the bile ducts and portal venules. In addition to obstructing biliary and venular flow, such a mechanism could also greatly reduce the total capacity of the voluminous portal venous network throughout the liver.

The total volume of blood within the splancnic vasculature accounts for at least 20% of the total blood volume and probably substantially more.\textsuperscript{18} The method employed in this study to measure it depends upon the dispersion of RISA within the splanchic vessels during equalization of radioactivities in the arterial and hepatic venous blood in the course of 60 to 90 seconds following intravenous injection. This period of equilibration is too short for movement of the tracer into sequestered pools of blood (as in splenic pulp) by diffusion so that the measurement must relate only to blood in vessels where the circulation is brisk and admixture rapid. Hence, it is not surprising that mean splanchnic circulation time (MCT) and SBV (properly referred to as circulating splanchic blood volume) are not affected in the dog by splenectomy. The reduction in MCT and SBV in association with portal hypertension and splenomegaly observed in these patients with hepatitis is therefore consistent with simultaneous contraction of the volume of well-mixed, actively circulating blood and expansion of the volume pent in the spleen and other portions of the splanchic vasculature. Anatomic studies suggest that some 60% or more of SBV is to be found within the intrahepatic portal and hepatic venous distributions and the sinusoids.\textsuperscript{18} It may be inferred that the changes produced by hepatitis are attributable either to venoconstriction or to compression of vessels in the portal tracts and the diseased hepatic parenchyma. Hepatomegaly does not appear to depend upon an increase in intrahepatic blood volume, though the possibility that hemorrhage or trapping may contribute importantly to the liver mass cannot be definitely eliminated.

The evidence that postsinusoidal resistance to hepatic venous outflow is unaffected by viral hepatitis is somewhat difficult to reconcile with the view\textsuperscript{1} that swollen liver cells may encroach upon and reduce sinusoidal perfusion. The location of the major point of resistance in the postsinusoidal vessels is uncertain. Increased values for WHVP in cirrhosis are correlated with marked focal compression or occlusion of central, sublobular, and small hepatic veins by expanding nodules of regenerating parenchymal cells. If compression of these veins occurs at all in hepatitis, it is presumably more diffuse than in cirrhosis, and distortion is less marked at the stage of the disease at which measurements were made in this study. At the level of the sinusoids the resistance is probably negligible and well-buffered by the rich array of lateral anastomoses and by the resulting availability of a large fraction of channels.
that are ordinarily "inactive." In addition, uniform swelling of hepatic cell plates in all three dimensions would tend to enlarge the sinusoidal lumina, thus offsetting to some extent the obstructive effect of localized necrosis with collapse. The more voluminous portions of the hepatic venous drainage system which would be involved in any change in SBV would contribute but little to outflow resistance.

With more severe disease it is likely that a basic heterogeneity of the anatomic and functional lesions becomes more profound and more easily detectable than it was in the series reported here. Certainly the normal values obtained for hepatic arterial-hepatic venous oxygen concentration differences could be construed as evidence of maintenance of a uniform perfusion of the metabolizing cell mass. The failure to extract BSP could also be attributed to a failure in cellular transport and bile formation rather than to a diversion of perfusate from the cells. This is so because the continued extraction of CA\textsubscript{131}I and ICG at levels approximating 65% of normal for both indicates perfusion of at least the same percentage of the parenchyma—if it were functioning normally. And since it was not, the reduction in phagocytosis and dye uptake is much more reasonably ascribed to a generalized cellular injury without marked change in the distribution of blood flow. It is evident from these data that the rapid recovery of BSP storage capacity observed in most patients with hepatitis 2 to 3 weeks after onset\textsuperscript{6} must be accounted for by recuperative changes in cellular function rather than by restoration of blood flow with improved delivery of BSP to the cells. Of considerable interest, too, is the fact that oxygen consumption appears to remain within normal limits despite the marked enlargement of the liver. Nor is there any evidence of change as hepatic function begins to recover, and hepatomegaly to regress. These findings suggest that acute hepatitis may be characterized by a uniform alteration in hepatocellular permeability and water content. Nevertheless, the liver in fatal hepatitis does present a remarkably varied pathological picture of irregular zonal necrosis, scattered hemorrhages, areas of massive cell death, and islets of viable tissue, all seemingly referable to corresponding changes in local circulatory integrity.\textsuperscript{1} More precise studies of the patterns of flow and volume distribution within the liver are necessary to determine if a less obvious hepatic hemodynamic heterogeneity also plays a pathogenetic role in the early stages of the acute disease.

**Summary**

Hepatic blood flow (EHBF) was measured by the clearance-and-extraction method using indocyanine green (ICG) in 15 patients hospitalized with acute viral hepatitis. In 10, the single injection technique (corrected for hepatic extraction and mean splanchnic circulation time, colloidal denatured human serum albumin-labeled with radiiodine, CA\textsubscript{131}I) was employed simultaneously to estimate flow (CABF).

Despite considerable clinical diversity (plasma bilirubin ranging, for example, from 2.4 to 32.0 mg%), EHB\textsuperscript{6} fell within normal limits (930 to 2,130 ml per min) in all but two patients (A.V., 890 ml per min and C.G., 2,430 ml per min), and was in good agreement with CABF. Although hepatic extraction of sulfobromophthalein was so greatly reduced (less than 10%) that it could not be employed for estimating EHB\textsuperscript{6}, both ICG and CA\textsubscript{131}I extractions were well maintained (21 to 73%, normal 63%, and 50 to 76%, normal 95%, respectively). Extraction of ICG returned to normal levels as jaundice cleared whereas CA\textsubscript{131}I extraction remained depressed indicating improvement in hepatocellular function without redistribution of blood flow within the liver during recovery.

Since the liver was obviously enlarged in all patients and since measurements of circulating splanchnic blood volume by the regional dilution method fell below the normal mean in eight of 10 patients, it was inferred that hepatomegaly was a result of augmented cell mass rather than vascular engorgement and that hepatic blood flow decreased relative
to tissue volume. Splanchnic oxygen arteriovenous difference and oxygen uptake also fell within normal limits in five patients suggesting that the increment in liver mass might be ascribed chiefly to cellular hydration.

Normal values for wedged hepatic venous pressure (10 patients) indicated that post-sinusoidal resistance remained unaltered and that cellular swelling did not affect post-sinusoidal resistance or perfusion. The observation reported by other workers that portal venous pressure may increase during the course of acute viral hepatitis must, therefore, be attributed to an increase in pre-sinusoidal portal venular resistance. It was concluded that inflammatory infiltration and increased capillary permeability within the portal tracts may contribute to the disease process by interfering both with portal venous inflow and biliary outflow.

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