Effects of Acute, Passive Hepatic Congestion on Blood Flow and Oxygen Uptake in the Intact Liver of the Cat

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SUMMARY Raising the hepatic venous pressure experimentally duplicates the type of hepatic congestion seen in many clinical situations including congestive heart failure. Venous pressure was controlled using a hepatic venous long circuit preparation and was raised by 6 cm blood (4.7 mm Hg) or 10 cm (7.8 mm Hg). Total splanchnic blood flow and oxygen uptake were reduced by these maneuvers but hepatic arterial flow was not altered nor was hepatic oxygen uptake. Blood flow in the portal vein decreased to 65 ± 12% of control and gut oxygen uptake decreased to 60 ± 14% of control. The data confirm that raised hepatic venous pressure does not produce hepatic edema in spite of massive prolonged fluid filtration across the liver into the peritoneum. In spite of a reduced (to 84 ± 3% of control) hepatic oxygen delivery, the liver can maintain oxygen uptake (99 ± 7% of control) by increasing oxygen extraction to appropriate levels. The hepatic artery in these cats was capable of myogenic vasoconstriction in response to altered arterial pressures, but in response to raised venous pressure no tendency for constriction was seen. This is in marked contrast to the vasoconstriction seen in isolated perfused livers where portal blood flow is held constant during the raised venous pressure.

CONGESTION of the hepatic circulation leads to a number of serious clinical conditions. Unfortunately, hepatic congestion is not uncommon. It occurs both during hepatic failure and secondarily during congestive heart failure. A great many studies have been done in an attempt to understand the underlying problems that occur in these conditions. A number of hypotheses have been forwarded to account in part or in whole for the abnormalities in hepatic function subsequent to hepatic congestion.

Brauer et al.1 concluded that “liver function is affected partly by the barrier to oxygen transfer imposed by the edema fluid. . . .” Further hemodynamic impairment of oxygen delivery to the liver is suggested by the observed decreases in hepatic blood flow shown to occur in isolated preparations1-2 and clinically.3 Metabolism of a variety of substances is reduced during heart failure and liver disease.4-6 The reduced hepatic metabolism could be due to hypoxia, diffusion impairment or simply to reduced blood flow.

In a recent review, Dunn et al.7 concluded that “The critical pathogenic factor appears to be hepatic hypoxia which causes centrolobular damage.” In the present paper I report the effects of acute elevation of hepatic venous pressure on hepatic hemodynamics and hepatic oxygen uptake in an attempt to evaluate the role of hypoxia in acute passive hepatic congestion.

Methods

Cats were anesthetized with ip injections of pentobarbital sodium (30 mg/kg). The method used to simultaneously measure hepatic oxygen uptake as well as hepatic arterial and total hepatic blood flow has been described in detail. Briefly, the method involves recording the hepatic arterial flow with a noncannulating electromagnetic flow probe and cannulation of the inferior vena cava in the thorax to measure total liver blood flow enroute to an extracorporeal reservoir. The inferior vena cava is occluded below the liver and the caval blood below the occlusion flows in a retrograde manner to drain via femoral vein cannulas into the reservoir where the blood is warmed and pumped back to the cat via cannulas in the jugular veins. The spleen is removed. The hepatic nerves are isolated from around the hepatic artery and cut. The cats respire unassisted. Hepatic oxygen uptake is calculated using the oxygen content in the hepatic artery, portal vein, and hepatic vein in conjunction with hepatic arterial flow and portal venous flow. Hepatic venous pressure is controlled by the outlet level of the hepatic venous cannula. Control levels were set approximately at the level of the right atria. Raising the outlet level produced a rise in hepatic venous pressure. Full details on the method of calculation, sampling of blood, and evaluation of the preparation are given elsewhere.

Results

Hepatic venous pressure was raised on 13 occasions in 11 cats by 6 cm or 10 cm blood (4.7 or 7.8 mm Hg). Table 1 shows the mean ± se of control values measured immediately before pressure elevation and the response seen when hepatic venous pressure was elevated by 4.7 mm Hg for 5-7 minutes on nine occasions. The values seen during raised venous pressure are expressed as the

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percent of the control values. Significance was calculated using Student's *t*-test for paired data. Control values of these and other parameters such as blood gases and blood pressures were similar to those described and discussed in detail previously using this and other methods. 

While total hepatic blood flow was reduced to 85% of control, on no occasion did the hepatic artery show significant changes in conductance. To verify that the present methodology did not abolish myogenic constriction of the hepatic artery, the liver was denervated and the response to bilateral carotid arterial occlusion was examined. The hepatic artery constricted in response to the elevated arterial pressure and the degree of constriction was highly correlated with the extent of arterial pressure rise (*r* = 0.94). In the intact denervated liver, raised hepatic venous pressure did not produce myogenic vasoconstriction.

Portal blood flow was, however, significantly reduced due entirely to decreased conductance in the splanchic organs feeding into the portal vein. Because the spleen was removed in this preparation, roughly 80% of the portal blood flow was derived from the intestines. The regions draining into the portal vein are referred to as the "gut" for convenience. Whereas gut conductance dropped to 65%, it may be significant to note that four animals showed no marked decrease in gut conductance. Attempts to ascertain reasons for the variability in gut responses proved futile.

Total splanchnic blood flow and oxygen uptake are frequently determined clinically. These values are shown in Table 1. The mean levels of total splanchnic oxygen uptake and vascular conductance were reduced by passive vasoconstriction.

Table 1: Effect of Raised Hepatic Venous Pressure (4.7 mm Hg) on Hemodynamics and Oxygen Uptake of Liver and Gut (n = 9)

<table>
<thead>
<tr>
<th>Vascular parameter</th>
<th>Control</th>
<th>% of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total blood flow (ml·min⁻¹·kg⁻¹)</td>
<td>27.1 ± 2.4</td>
<td>85 ± 4.4*</td>
</tr>
<tr>
<td>Hepatic arterial flow (ml·min⁻¹·kg⁻¹)</td>
<td>14.5 ± 1.8</td>
<td>99 ± 2.2</td>
</tr>
<tr>
<td>HAF/HBF (%)</td>
<td>53 ± 3.8</td>
<td>120 ± 8.6*</td>
</tr>
<tr>
<td>Hepatic arterial conductance (ml·min⁻¹·kg⁻¹·mm Hg⁻¹)</td>
<td>0.117 ± 0.016</td>
<td>99 ± 2.4</td>
</tr>
<tr>
<td>Portal flow (ml·min⁻¹·kg⁻¹)</td>
<td>12.6 ± 1.6</td>
<td>65 ± 12*</td>
</tr>
<tr>
<td>Portal conductance (ml·min⁻¹·kg⁻¹·mm Hg⁻¹)</td>
<td>2.06 ± 2.5</td>
<td>101 ± 2.2</td>
</tr>
<tr>
<td>Portal pressure (mm Hg)</td>
<td>6.2 ± 0.3</td>
<td>126 ± 3.4*</td>
</tr>
<tr>
<td>Gut conductance (ml·min⁻¹·kg⁻¹·mm Hg⁻¹)</td>
<td>0.108 ± 0.02</td>
<td>65 ± 12*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oxygen parameters</th>
<th>Control</th>
<th>% of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic O₂ delivered (ml·min⁻¹·kg⁻¹)</td>
<td>2.2 ± 0.4</td>
<td>84 ± 3.3</td>
</tr>
<tr>
<td>Hepatic O₂ uptake (ml·min⁻¹·kg⁻¹)</td>
<td>1.1 ± 0.1</td>
<td>97 ± 6.9</td>
</tr>
<tr>
<td>Hepatic O₂ extract (%)</td>
<td>58 ± 8</td>
<td>117 ± 11</td>
</tr>
<tr>
<td>Hepatic O₂ delivered (ml·min⁻¹·kg⁻¹)</td>
<td>1.3 ± 0.1</td>
<td>58 ± 12.9*</td>
</tr>
<tr>
<td>Gut O₂ uptake (ml·min⁻¹·kg⁻¹)</td>
<td>0.8 ± 0.01</td>
<td>60 ± 13.6*</td>
</tr>
<tr>
<td>Gut O₂ extract (%)</td>
<td>65 ± 3.7</td>
<td>101 ± 2.8</td>
</tr>
</tbody>
</table>

Total splanchnic
- Oxygen uptake (ml·min⁻¹·kg⁻¹) | 1.9 ± 0.1 | 79 ± 5.6* |
- Conductance (ml·min⁻¹·kg⁻¹·mm Hg⁻¹) | 0.160 ± 0.029 | 85 ± 4.4* |

*Statistical significance *P* < 0.05 according to Student's *t*-test for paired data. The data in the control column show mean values while the second column shows the percent of control value of the parameters measured 5-7 minutes after hepatic venous pressure was raised by 4.7 mm Hg (6 cm blood). HAF/HBF (%) represents the proportion of hepatic blood supply derived from the hepatic artery in this splenectomized preparation.
RAISED VENOUS PRESSURE AND HEPATIC O₂ UPTAKE/Laust

equal to 47% of the venous pressure increase. Total flow was decreased to 83 ± 7% and 78 ± 9% of control at 5 and 15 minutes, respectively.

Discussion

The sort of hepatic congestion experimentally produced by raising hepatic venous pressure is similar to hepatic congestion seen during congestive heart failure, postsinusoidal intrahepatic block (Laennec's and postnecrotic cirrhosis), or extrahepatic postsinusoidal obstruction (Budd-Chiari syndrome).

The use of the hepatic venous long circuit preparation for obtaining hemodynamic and metabolic data from an intact liver has previously been described and evaluated.8 Raising hepatic venous pressure by elevating the level of the outlet of the cannula draining the hepatic venous blood has been used as a model for acute, passive hepatic congestion in studies related to fluid exchange.10-12 Compliance,13 and precapillary sphincters14 in the intact liver of cats. The present paper describes the effects of passive hepatic congestion on hepatic hemodynamics and oxygen uptake.

In a recent review Dunn et al.7 listed the pathogenic factors thought to be responsible for hepatic changes in congestive heart failure. The factors described included decreased hepatic blood flow with resultant decrease in hepatic oxygen supply as well as pressure atrophy of liver cells and edema (both leading to cellular hypoxia). Few studies have been done of the sort required to elucidate the possible role of such factors.

Partial occlusion of the inferior vena cava has been shown to produce a progressive hepatic necrosis and fibrosis similar to that seen clinically.15 Unfortunately, the extent of pressure elevation or portal hypertension was not measured. Brauer et al.16 reported that raising hepatic venous pressure by 1 cm H₂O produced congestion and appearance of exudate on the liver surface. When venous pressure was raised to 5 cm H₂O, the lobular architecture was no longer recognizable. If venous pressure was increased to 10 cm, there was evidence of structural disruption. They reported that filtration and edema formation reached near maximum levels at 7 cm H₂O. The observation of edema in their experiments and the suggestion that it plays an important role in the pathophysiology of passive congestion have greatly influenced current attitudes. However, their data were obtained in isolated rat liver perfused only through the portal vein. Similar edema in the isolated dog liver perfused through both inlet vessels did not occur.2 The use of isolated perfused liver for hemodynamic studies has previously been criticized.8 Raised hepatic venous pressure produces massive, prolonged, and constant filtration of fluids across the hepatic sinusoids.10,11 Fluids leave the sinusoid and enter the space of Disse making relatively unimpeded passage through Glissons capsule and into the peritoneal spaces. The first droplets of filtrate appear well before 5 minutes after the venous pressure is raised. If tissue hydrostatic pressure is to be elevated and edema present, it should appear at that early time. Rather than the impaired oxygen uptake predicted by decreased diffusion of oxygen, the hepatic uptake of oxygen is well maintained. This is in spite of a reduced oxygen delivery to the liver. These data further support the conclusion that hepatic edema does not occur in response to raised venous pressure.10,11 To test this hypothesis more rigorously, hepatic venous pressure was increased to 10 cm blood (7.8 mm Hg) and parameters were measured at 5 and 15 minutes. No impairment of oxygen uptake occurred; hepatic extraction increased to compensate for the reduced blood flow. Increases in interstitial hydrostatic pressure would furthermore be expected to result in added impedance to flow in the low resistance vessels of the portal vein. Following the initial rapid (within 15 seconds) increase in portal pressure seen with raised hepatic venous pressure, no further changes in intrahepatic portal vascular conductance were seen at either pressure tested. This also suggests that changes in interstitial fluid pressure do not progress past the initial rapid increment and that accumulation of edema fluid does not occur.

THE HEPATIC ARTERY

In an isolated, perfused dog liver, raising hepatic venous pressure 9 mm Hg produced a marked increase in hepatic arterial resistance.7-10 The cats used in the present study showed myogenic constriction to raised arterial pressure but not to raised venous pressure. Conductance remained 99 ± 2.4% of control levels when pressure was raised by 6 cm H₂O (4.7 mm Hg). Even at pressure increments of 10 cm blood (7.8 mm Hg), hepatic arterial conductance was 88% of control. In the isolated preparations, portal venous flow was held constant during raised venous pressure. In the present study, portal blood flow was significantly reduced (to 65 ± 12% of control level). Factors controlling hepatic arterial blood flow are still unknown but decreased portal flow is reported to produce a rise in arterial blood flow.9,16 The reduced portal flow, however, cannot account entirely for the lack of constriction of the hepatic artery since portal flow changes varied widely (from 100% to as low as 13% of control) while arterial conductance showed surprisingly consistent responses. The decrease in hepatic blood flow seen with hepatic cirrhosis is also estimated to be primarily due to decreased portal blood flow.17

It is interesting that the lack of presinusoidal constriction is seen in the liver where we have previously demonstrated that vasodilation (i.a. histamine or isoproterenol) or vasoconstriction (nerve stimulan or noradrenaline) do not alter hepatic fluid exchange.18-20 In these articles and in a recent review of related concepts,18 I have described experiments which indicate strongly that vascular events in the presinusoidal vessels do not influence capillary pressure or effective surface area available for fluid exchange. Teleologically speaking, constriction of the hepatic artery during raised venous pressure would not therefore afford protection against fluid filtration and would in fact be a useless and detrimental response due to reduction of oxygen supply. In skeletal muscle18,21 and gut,22 the constriction of precapillary sphincters and resist-
ance vessels does occur and is a useful response preventing massive fluid filtration.

PRESINUSOID SPHINCTERS

In a similar manner I have demonstrated that, while presinusoidal sphincters in the liver do not appear to affect fluid exchange, they can alter hepatic oxygen extraction. It was suggested that the sphincters are influenced by blood flow in the hepatic artery and insignificantly affected by myogenic effects. Oxygen extraction can be shown to be reduced by sphincter-like constriction in the liver. The lack of even minor impairment of oxygen uptake suggests that sphincters were not constricted by the raised venous pressure. Oxygen extraction appeared to be coupled only to the supply-to-demand ratio within the sinusoids; the decreased oxygen delivery was compensated for adequately to prevent any changes in oxygen uptake.

HEPATIC DYSFUNCTION

Safram and Schaffner, using electron microscopic analysis of human biopsy material, concluded that the increased pressure produced prolonged changes in hepatic structure such as flattening of the liver plates and disappearance of surface microvilli and that anoxia did not appear to play an important role. In chronic congestion there is usually a reduced cardiac output which would further add to the magnitude of the hepatic flow reduction. Cellular hypoxia resulting from decreased cardiac output or during exercise in conjunction with hepatic congestion cannot be eliminated as a possible source of hepatic damage and dysfunction. Desaturation of arterial blood during congestive episodes has been suggested as a further complication rather than a primary cause of hepatic dysfunction.

In conclusion, hepatic cellular disruption seen in chronic passive congestive failure is unlikely to be due to hypoxia related to edema formation or hemodynamic changes directly due to the pressure increment within the liver. Whereas decreased blood flow will reduce clearance rates of many endogenous substances, the reduced flow will have little direct consequence to the liver since hepatic oxygen uptake can be maintained by large increases in extraction of oxygen. A more reasonable causative factor might be the effect of pressure on the hepatic architecture resulting in local disruption of the hepatocytes, although experimental data to support this concept are not available.

Acknowledgments

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