Effect of Pitressin on the Splanchnic Circulation in Man

By Stanley Shaldon, M.D., Wolfgang Dolle, M.D., Luis Guevara, M.D., Frank L. Iber, M.D., and Sheila Sherlock, M.D.

Posterior Pituitary Extract is known to lower the portal venous pressure in animals,1,2 and in man a similar effect has been demonstrated during the control of bleeding from esophageal varices with intravenous pitressin.4-6 It has been suggested that pitressin lowers portal pressure by increasing splanchnic resistance.7

The present communication concerns the effects of intravenous pitressin on splanchnic hemodynamics in control subjects and in patients with liver disease. The patients included some with cirrhosis in whom the portal vein was patent and some with a surgical portacaval anastomosis. Patients with normal liver structure but with occlusion of the portal vein were also studied. It was thus possible to study the effects of pitressin upon the splanchnic hemodynamics as a whole, and also upon the liver hemodynamics independent of the splanchnic bed in patients in whom portal venous blood was totally diverted from the liver.

Methods

The patients were divided into three groups. Group 1 consisted of four subjects without liver disease, group 2 consisted of 10 patients with portal cirrhosis in whom splenic venography had confirmed that the portal vein was patent. These patients had varying degrees of portal hypertension. Group 3 consisted of 11 patients with portal cirrhosis and a patent end-to-side portacaval anastomosis confirmed by splenic venography, and two patients in whom splenic venography showed a blocked portal vein and who had a normal liver biopsy.

Estimation of Hepatic Blood Flow

A size-9 radiopaque cardiac catheter was introduced into one of the main right hepatic veins under fluoroscopic control. The catheter was positioned freely in the central portion of the right lobe of the liver and the exact site of the tip was observed. If the catheter was advanced for a wedged hepatic venous pressure determination, it was subsequently repositioned in the previous “free” sampling position. After an initial priming dose of 20 to 40 mg. of bromsulphalein (BSP), a constant infusion of BSP varying from 1.5 to 4.0 mg. per minute was given intravenously from a Sigma pump attached to a calibrated burette. Paired blood samples for BSP analysis5 were withdrawn at 10-minute intervals from the hepatic vein catheter and an indwelling needle in a femoral artery. A minimum of three pairs of samples was obtained for estimation of basal hepatic blood flow, which was calculated by Fick principle, with the correction formula for changing arterial levels of BSP when required.9

Pressure Determination

The mean arterial pressure (MAP) was calculated from the formula:

MAP mm. Hg. = diastolic pressure + 1/3 pulse pressure (recorded at 2-minute intervals with a sphygmomanometer).

The wedged hepatic venous pressure (WHVP) was measured by advancing the hepatic vein catheter into the wedged position,10 the free hepatic venous pressure (FHVP) was recorded after the abrupt drop in pressure in the wedged position when the catheter lay freely in a main hepatic vein.

Serial intrasplenic pressures (ISP) were recorded after percutaneous splenic puncture11 and the introduction of a polythene catheter into the spleen.12

All pressures were recorded with an Elema-Schonander electromanometer with zero reference point situated 5 cm. below the sternal angle. Mean pressure measurements were calculated by planimetry to the nearest 0.5 mm. Hg from electrically damped tracings showing minimal respiratory fluctuations. Pressures were recorded before the start of the BSP infusion and at the end of the basal period, 20 minutes after starting the pitressin infusion and on at least two subsequent occasions in the following 40 minutes, and if the BSP was continued to beyond 60 minutes from starting pitressin on three to four subsequent occasions. In certain patients pressure recordings

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Table 1

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<tr>
<th>Group</th>
<th>Case no.</th>
<th>WHVP 1 mm. Hg (%)</th>
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<th>ISP 1 mm. Hg (%)</th>
<th>PVP 1 mm. Hg (%)</th>
<th>MAP 1 mm. Hg (%)</th>
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Means of percentage change: -38.7
S.D.: 7.2

Pressure gradient mm. Hg $\times 80 = $

\[
\text{Blood flow L. per minute} = \frac{\text{Resistance (dynes sec. cm.}$^2$)}{
\text{Postsinusoidal resistance (PSR) defined as the resistance to hepatic venous outflow was calculated from the formula:}
\[
\text{PSR dynes sec. cm.}^2 = \frac{\text{WHVP} - \text{FHVP} \times 80}{\text{EHBF L. per min.}}
\]

Splanchnic resistance (SR) defined as the arteriolar resistance to inflow of blood to the splanchnic

References

**Resistances**

Resistances were calculated from a modification of Poiseuille's law. 

\[
PVP^c \text{ mm. Hg} = \frac{\text{ISP} + \text{WHVP}}{2}
\]

Postsinusoidal resistance (PSR) defined as the resistance to hepatic venous outflow was calculated from the formula:

\[
\text{PSR dynes sec. cm.}^2 = \frac{\text{WHVP} - \text{FHVP} \times 80}{\text{EHBF L. per min.}}
\]

EHBF = estimated hepatic blood flow.

Splanchnic resistance (SR) defined as the arteriolar resistance to inflow of blood to the splanchnic
### Effects of Pitressin on Splanchnic Hemodynamics in All Groups

<table>
<thead>
<tr>
<th>EHBF</th>
<th>PSR</th>
<th>SR</th>
<th>HAR</th>
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<tr>
<td>ml. per min.</td>
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<td>680</td>
<td>1,020</td>
<td>-34</td>
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\[ \text{SR dynes sec. cm}^{-1} = \frac{\text{MAP} - \text{PVP} \times 80}{\text{EHBF L. per min.}} \]

In some patients with a patent portal vein (groups 1 and 2) the intrasplenic pressure was not measured, and consequently the splanchnic resistance was calculated from the MAP-WHVP pressure gradient. Hepatic arteriolar resistance (HAR) defined as the resistance to the inflow of blood to the liver via the hepatic artery alone, in patients in whom portal venous blood was totally diverted from the liver (group 3) was calculated from the formula:

\[ \text{HAR dynes sec. cm}^{-1} = \frac{\text{MAP} - \text{WHVP} \times 80}{\text{EHBF L. per min.}} \]

**Procedure**

Twenty units of pitressin (Parke-Davis) (diluted in 100 ml. of 5 per cent dextrose) were infused intravenously over a 10-minute period. During the pitressin infusion and for a further 10 minutes after completion of the infusion, (0 to 20 minutes), no samples of blood were taken. After this time interval further paired samples of arterial and hepatic venous blood were obtained for BSP analysis at 10-minute intervals up to 60 minutes following the commencement of the pitressin infusion (20 to 60 minutes). In certain patients the sampling was extended to 100 minutes after
and calculated resistances for the following time periods:

Period 1 = control period before pitressin infusion.

Period 2 = 20 to 60 minutes after commencing the pitressin infusion. [Only the mean arterial pressure was recorded during the pitressin infusion (0 to 10 minutes) and for the subsequent 10 minutes]

Period 3 = 60 to 100 minutes after commencing the pitressin infusion.

The results are expressed in absolute values and also as the percentage alteration of the parameters in period 2 as compared with period 1 except for the mean arterial pressure where the maximal increase (P) occurred during the pitressin infusion, and this increase is also expressed as a percentage of the baseline mean arterial pressure. Statistical analyses are confined to the percentage changes because the absolute variations among the groups are too large to permit a valid statistical assessment of the absolute measurements.

Patients without liver disease (Group 1).

In four control subjects the wedged hepatic venous pressure was reduced by an average of 4.5 mm. Hg during period 2. The percentage reduction averaged 40 per cent. The free hepatic venous pressure was reduced by an average of 35 per cent. In two of these patients the intrasplenic pressure fell by 5.5 mm. Hg representing a 45 and 47 per cent reduction and the calculated portal venous pressure fell by a similar amount. The maximum increase in mean arterial pressure occurred during the pitressin infusion and averaged 30 per cent but the systemic blood pressure had returned to baseline levels in all cases before period 2. In three control patients estimated hepatic blood flow was reduced by an average of 660 ml. per min. representing a reduction of 45 per cent. The calculated splanchnic resistance averaged 4,450 dynes seconds cm.\(^{-5}\) in these three patients, and was increased by an average of 94 per cent during period 2. The postsinusoidal resistance averaged 260 dynes cm.\(^{-5}\) and was not consistently altered following the pitressin infusion (two subjects showed

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a slight reduction of 2 and 9 per cent and one subject showed an increase of 26 per cent). In one subject (no. 1, fig. 1) these measurements were extended to period 3 and all parameters had almost returned to baseline levels 80 minutes after commencing the pitressin.

Patients with portal cirrhosis and a patent portal vein (Group 2). In five patients the wedged hepatic venous pressure fell by an average of 10 mm. Hg representing a 36 to 54 per cent reduction during period 2. The free hepatic venous pressure was reduced by an average of 35 per cent. In seven patients (including two in whom the wedged hepatic venous pressures were measured simultaneously) the mean reduction in intrasplenic pressure was 43 per cent representing an absolute pressure reduction of 11.6 mm. Hg. The calculated portal venous pressure in two patients was reduced by 36 and 50 per cent during period 2. The maximum increase in mean arterial pressure occurred during the pitressin infusion and averaged 24 per cent, but had returned to baseline levels in all cases before period 2. In two patients estimated hepatic blood flow was reduced by 41 and 34 per cent respectively, representing an absolute reduction of 480 and 340 ml. per minute during period 2. The calculated splanchnic resistances during the control period in these two patients were 5,900 and 5,800 dynes seconds cm.\(^{-5}\) and there was an 83 and 68 per cent increase in these resistances during period 2. The postsinusoidal resistances during the control period were 1,200 and 1,240 dynes second cm.\(^{-5}\) and were virtually unaffected by the pitressin infusion. In one patient (no. 7, fig. 2) measurements were extended to period 3 and all parameters had returned to baseline levels by 80 minutes after starting the pitressin infusion.

In one patient (no. 28) 10 units of pitressin produced a 15 per cent reduction in wedged and free hepatic venous pressures, an 18 per cent reduction in estimated hepatic blood flow, and a 26 per cent increase in splanchnic resistance during period 2. The postsinusoidal resistance was not significantly altered, the effects lasted for a similar period of time to the 20-unit pitressin infusion.

Patients with total diversion of portal blood from the liver (Group 3).

Patients with portal cirrhosis and a patent portacaval anastomosis. In nine patients the wedged hepatic venous pressure was reduced by an average of 5.6 mm. Hg during period 2. The percentage reduction averaged 36 per cent; the free hepatic venous pressure was reduced by an average of 31 per cent. In nine
patients (including seven in whom the wedged hepatic venous pressure was measured simultaneously) the intrasplenic pressure fell by an average of 38 per cent, representing an absolute reduction of 4.5 mm. Hg. The maximum increase in mean arterial pressure occurred during the pitressin infusion and averaged 14 per cent. Arterial pressures had returned to baseline levels in all patients by the start of period 2. In six patients the estimated hepatic blood flow fell by an average of 38 per cent. The absolute reduction in flow averaged 290 ml. per minute.

The hepatic arteriolar resistance in six patients averaged 8,000 dynes seconds cm.\textsuperscript{-5} during the control period and was increased by an average of 60 per cent during period 2. The postsinusoidal resistance averaged 1,200 dynes seconds cm.\textsuperscript{-5} in the control period and was not consistently altered following the pitressin infusion (two patients showed no change, two patients showed a reduction of 5 and 15 per cent, and two patients had an increase of 5 per cent in postsinusoidal resistance). In one patient (no. 22, fig. 3) measurements were extended to period 3 and all parameters had almost returned to baseline about minutes after the start of the pitressin infusion.

Patients with portal venous thrombosis and a normal liver. In two patients the wedged hepatic venous pressures fell by 38 and 33 per cent respectively. The free hepatic venous pressures were reduced by 25 and 40 per cent (fig. 4). The simultaneously determined intrasplenic pressures fell by 59 and 43 per cent, representing an absolute reduction of 13 and 12 mm. Hg. The maximum increases in arterial pressures were seen during the pitressin infusion and were 20 and 13 per cent respectively. Estimated hepatic blood flows were reduced by 43 and 36 per cent. The hepatic arteriolar resistances in the control period in these two patients were 6,100 and 11,200 dynes sec. cm.\textsuperscript{-5} respectively and were increased by 77 and 62 per cent during period 2. The postsinusoidal resistances were 290 and 320 dynes seconds cm.\textsuperscript{-5} in the control period and were not significantly altered during period 2.

Combined Results for All Groups

The mean percentage alterations during period 2 following 20 units of pitressin for
the various parameters for all groups were determined. The wedged hepatic venous pressure was reduced by 38.7 ± 7.2 per cent, the free hepatic venous pressure was reduced by 33.1 ± 11.6 per cent, and the intrasplenic pressure was reduced by 41.9 ± 7.7 per cent for 20 patients. The estimated hepatic blood flow was reduced by 39.9 ± 6.1 per cent in 13 patients. The postsinusoidal resistance was increased by 0.76 per cent, which was not significantly different from zero (0.8 < p < 0.9). The splanchnic resistance in five patients with a patent portal vein (groups 1 and 2) increased by 86.6 ± 12.7 per cent. The hepatic arteriolar resistance in eight patients with a total diversion of portal blood flow to the liver (group 3) was increased by 77.5 ± 20.4 per cent. There was no significant difference between the mean increase in splanchnic resistance in control and cirrhotic patients or the mean increase in hepatic arteriolar resistance in patients with cirrhotic or normal livers and total diversion of portal venous blood. Similarly there was no significant difference between the groups in the percentage changes in parameters induced by pitressin except for the smaller increase in mean arterial pressures seen in group 3. The percentage changes were all in the same direction in the patient who received 10 units of pitressin but were lower than the 95 per cent lower limits of the changes induced by 20 units of pitressin.

Side Effects

Most patients experienced abdominal discomfort with cramp sensations and evacuation of the bowels during the pitressin infusion and also tightness of the skin with marked facial pallor. These side effects passed off rapidly and were not present during the measurements made in periods 2 and 3.

Discussion

The validity of the calculation of resistance in the splanchnic circulation is dependent upon several assumptions. The abrupt drop in pressure seen on withdrawing a catheter from the wedged hepatic position suggests that the site of resistance to hepatic venous outflow is located at the site of pressure drop. The wedged hepatic venous pressure is almost certainly a measure of hepatic sinusoidal pressure and its close agreement with the directly recorded portal venous pressure depends upon the free flow of portal blood from the portal vein to the hepatic sinuses, through a low-resistance circuit. In the presence of obstruction to portal venous flow or surgical diversion of portal blood through a portacaval anastomosis, the wedged hepatic venous pressure is no longer related to the portal pressure and reflects only the hepatic sinusoidal pressure. Hence the site of resistance to hepatic venous outflow may be located anywhere between the sinuses and the main hepatic veins. The anatomic location of this resistance does not detract from the validity of calculating the resistance from the pressure gradient and the estimated hepatic blood flow. The gradient between the free hepatic vein pressure and the inferior vena caval pressure rarely exceeds 1 mm. Hg and so adds little to the postsinusoidal resistance. The calculation of splanchnic resistance is dependent upon the assumption that estimated hepatic blood flow equals splanchnic blood flow, and that the measured indirect portal pressure corresponds to the pressure on the venous side of the mesenteric vessels. In the absence of a portal collateral circulation, hepatic blood flow must equal splanchnic blood flow. If a portal collateral circulation exists as in the two patients in group 2, the calculated splanchnic resistance is overestimated. Nevertheless, the percentage changes induced by pitressin are probably valid measures of the changes in splanchnic resistance even if the absolute measurements are overestimated. In order to determine the best estimate of portal venous pressure, a mean of the intrasplenic and wedged hepatic venous pressures was used if both were available and the portal vein was unobstructed and in functional continuity with the liver.

The concept of hepatic arteriolar resistance was introduced to estimate the resistance to inflow of hepatic arterial blood to the liver in patients in whom portal venous blood was totally diverted from the liver. If the wedged

*± = One standard deviation.
hepatic venous pressure measures hepatic sinusoidal pressure, then this calculated resistance is valid. In these patients the mesenteric component of the splanchic resistance could not be calculated as the blood flow in the portal vein was not measured, but the pressure in the portal circuit was measured by splenic pressure recordings and changes in this pressure were interpreted as indexing changes in mesenteric arteriolar resistance.

The mechanism whereby pitressin lowers the portal pressure is related to the increase in calculated splanchic resistance in patients with an intact portal vein. In patients with total prehepatic deviation of portal blood the reduction in portal pressure (ISP) was of a similar degree to that observed in patients with a patent portal vein and suggests therefore that the mesenteric arteriolar resistance was increased as well as the hepatic arteriolar resistance in these patients. The similarity of response in patients with and without cirrhosis, suggests that pitressin affects the mesenteric arterioles of the cirrhotic and non-cirrhotic patient to a similar degree. It is therefore unlikely that functional arterial venous anastomoses in the mesentery are operative in the pathogenesis of portal hypertension in cirrhosis as has been suggested by Levey and Gliedman. A vasoconstrictor agent would have a smaller effect on an arteriovenous anastomosis than upon an arteriolar capillary venous circuit.

In patients with total prehepatic deviation of portal blood, pitressin reduced the hepatic blood flow by an increase in the hepatic arteriolar resistance. There was no significant difference in the basal hepatic arteriolar resistances of the cirrhotic and noncirrhotic patients with no portal blood flowing to the liver (group 3), or in the per cent increase in hepatic arteriolar resistance following the pitressin infusion. This latter observation suggests that hepatic arteriolar sinusoidal anas-

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Figure 4

The effect of 20 units of pitressin on the splanchonic hemodynamics—patient (no. 26) with a portal vein thrombosis and a normal liver (group 3). Estimated hepatic blood flow was reduced by 41 per cent and the wedged hepatic venous pressure fell by 38 per cent. Hepatic arteriolar resistance was increased by 77 per cent, while the postsinusoidal resistance was not affected during period 2. The intrasplenic pressure was reduced by 59 per cent during period 2.
tomoses are consequently unlikely to be operative in the genesis of portal hypertension in patients with cirrhosis.

The reduction in hepatic arterial blood flow in patients with cirrhosis is undesirable, as morphologic evidence suggests that regeneration nodules derive their blood supply entirely from the hepatic artery. The repeated use of pitressin in clinical trials in the control of bleeding varices did not result in hepatic ischemia. Furthermore Davis and co-workers have shown that hepatic oxygen consumption is not reduced when hepatic blood flow is reduced by pitressin. The action of the intravenously administered pitressin on the splanchnic circulation did not exceed 1 hour and, as a therapeutic measure, this is obviously disadvantageous. The peripheral vasoconstrictor effect was even more transient, as the mean arterial pressure was elevated only during the pitressin infusion of 10 minutes’ duration.

The over-all circulatory effect of pitressin appears to be a redistribution of blood flow in the body, as the cardiac output is not altered. The reported increase in skeletal muscle blood flow probably accounts for the reduction in the skin, renal, and splanchnic blood flow. The hepatic venous blood outflow resistance (postsinusoidal resistance) was not altered, and this resistance may not be subject to vasoconstrictor effects in man.

In patients with cirrhosis the postsinusoidal resistance was raised above the control range of 244 ± 78 dynes seconds cm⁻⁵ established in this laboratory. The postsinusoidal resistance in cirrhosis may not be significantly reduced by a portacaval anastomosis, as all patients with cirrhosis and a portacaval anastomosis in group 3 had an elevated postsinusoidal resistance, and previous work showed no significant alteration in postsinusoidal resistance calculated in absolute units in 10 patients with cirrhosis before and after a portacaval anastomosis. The elevation of the postsinusoidal resistance in cirrhosis conforms morphologic opinions that the fundamental lesion responsible for portal hypertension in cirrhosis is an obstruction to hepatic venous outflow by constriction of the hepatic veins with regeneration nodules. The normal post-sinusoidal resistance in patients with an extrahepatic portal venous obstruction and a normal liver structure clearly demonstrated that portal hypertension in these cases is not related to intrinsic liver disease. If the postsinusoidal resistance is maintained by an organic reduction of the hepatic venous outflow tract, it is unlikely that drugs will affect this resistance. Previous workers have reported changes in hepatic blood flow or portal pressure under a variety of circumstances, and in all these conditions changes in the splanchnic resistance were implicated.

The elevated postsinusoidal resistance in cirrhosis is probably only reduced with prolonged medical treatment and diuretic therapy in patients with ascites or fatty livers. In these patients one may postulate a reduction in intrahepatic edema or fat as the mechanism whereby the hepatic venous outflow obstruction is reduced. One may therefore conclude that pharmacologically induced reductions in the portal pressure may only be achieved by increasing the splanchnic resistance, and pitressin is the most potent splanchnic vasoconstrictor available.

Summary

The effects of 20 units of pitressin administered intravenously on the splanchnic circulation in four patients without liver disease, 10 patients with cirrhosis and a patent portal vein, 11 patients with cirrhosis and an end-to-side portacaval anastomosis and two patients with an extrahepatic portal vein obstruction and a normal liver structure, were observed. Estimated hepatic blood flow and wedged hepatic venous and intrasplenic pressures were measured in all groups, and the hepatic, hepatic arteriolar, and hepatic postsinusoidal resistances were calculated. Pitressin reduced the portal pressure by an average of 39 per cent for 1 hour. Estimated hepatic blood flow was reduced by 40 per cent. Splanchnic resistance was increased by 87 per cent and hepatic arteriolar resistance by 77 per cent. Postsinusoidal resistance was not affected. The drop in portal pressure could be
related to the increases in splanchnic resistance. There was no difference in the response to pitressin between patients with cirrhosis and patients with normal liver structure and function. It is suggested that the fundamental lesion causing portal hypertension in cirrhosis is an obstruction to the hepatic venous outflow and that mesenteric and hepatic arteriolar venous anastomoses are not operative in the genesis of portal hypertension in cirrhosis. This obstruction to hepatic venous outflow is not alterable pharmacologically and any attempts to lower portal pressure by medical means must be achieved by alterations in the splanchnic resistance. Pitressin appears to be the most potent splanchnic vasoconstrictor available.

Acknowledgment
We wish to thank Dr. J. A. L. Gorringe, of the Parke Davis Company, for supplying the pitressin, and the Medical Research Council, the British Empire Cancer Campaign, and Messrs. G. D. Searle & Company Limited for financial assistance.

References


Biological thought has never attained to that finality which appears, at least by contrast, to characterize the greater body of opinions in physical science.

In particular two extreme views, though often commingled, have continually striven for the mastery. The one of these, purely scientific and wholly positive, declares the phenomena of life to be, while partly unknown, ultimately knowable as manifestations of matter and energy. According to this view life is a mechanism and nothing more, in its positive scientific aspects at least. Without necessarily denying such assertions, the other view sees the unique properties of life to be dependent upon an equally unique force or tendency, operating in or through its physico-chemical organization. Either there is a peculiar vital force; or there is manifest in the organism a peculiar tendency; or at any rate life patently follows the path into which it was propelled by an original impetus, peculiar to life, unknown in other phenomena. All such views inherently partake of metaphysics, and have, therefore, ever aroused most determined opposition among the more orthodox devotees of science.—Lawrence J. Henderson. The Fitness of the Environment. New York, The Macmillan Co., 1924, p. 282.
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