SPLEEN BLOOD FLOW AND SPLANCHNIC HAEMODYNAMICS IN BLOOD DYSCRASIA AND OTHER SPLENOMEGALIES

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SUMMARY

1. Splenic blood flow and splanchnic haemodynamics have been studied in twenty patients with splenomegaly due to blood dyscrasia or diseases involving the reticulo-endothelial system. Thirteen of these patients had portal hypertension, three had abdominal collaterals on arteriovenography and one oesophageal varices.

2. Total spleen blood flow was increased in all with values up to 1550 ml/min, and associated with this liver blood flows increased up to 2.61 l min⁻¹ m⁻². In four patients the cardiac output was raised.

3. In five patients a raised wedged hepatic vein pressure was found which was solely related to the increase in liver blood flow, but in two others, in whom hepatic histology was abnormal, there was also an increase in postsinusoidal resistance. Nine patients had a raised hepatic pre-sinusoidal resistance. This was related to a greatly increased liver blood flow with portal tract fibrosis and cellular infiltration as possible additional factors.

4. The haemodynamic findings in these patients were similar to those found previously in patients with tropical splenomegaly. In both groups spleen blood flow in ml 100 g⁻¹ min⁻¹ was inversely proportional to spleen size. There were similar increases in total spleen and liver blood flows and in the percentage of patients with an increased pre-sinusoidal resistance. In contrast, in cirrhosis there was no inverse relationship between flow in l 100 g⁻¹ min⁻¹, and of spleen size, and for the degree of splenomegaly total spleen blood flow was relatively greater.

In 1894 Banti suggested that an increased spleen and portal blood flow resulting from enlargement of the spleen might induce portal hypertension with secondary fibrosis and cirrhosis of the liver. This theory later fell into disrepute when it was demonstrated that in cirrhosis the major cause of portal hypertension was post-sinusoidal obstruction in the liver due to the

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pressure of regeneration nodules on hepatic venules. However, an increased spleen blood flow may be the primary cause in patients with unexplained portal hypertension and splenomegaly but without liver disease (Tisdale, Klatskin & Glenn, 1959; Perez, 1961) and in patients with tropical splenomegaly in whom no obstruction to portal or hepatic venous flow can be demonstrated (Williams et al., 1966). Furthermore, occasional patients with reticuloses and blood diseases with splenomegaly have been described in whom the portal hypertension was also unexplained (Rosenbaum, Murphy & Swisher, 1966).

Until recently there was no satisfactory method for measuring blood flow through the spleen except at operation. In 1968 Williams and his colleagues described a method based on the clearance of radioactive xenon from the spleen determined by surface counting which measured flow per 100 g of splenic tissue. Total flow could be calculated when the weight of the spleen became known later following splenectomy or at autopsy. Recently, however, Blendis, Williams & Kree1 (1969c) have been able to derive a regression equation relating the area of the spleen on an anterio-posterior radiograph to the logarithm of spleen weight, thus enabling total spleen blood flow to be calculated at the same time as the xenon flow measurement. In this paper we report measurements of spleen blood flow and hepatic haemodynamics in twenty consecutive patients with splenomegaly due to blood dyscrasia or diseases involving the reticulo-endothelial system. The flows per 100 g of tissue and the total flows are also compared with those previously found in patients with idiopathic tropical splenomegaly and cirrhosis.

MATERIAL AND METHODS

Clinical details of the twenty patients are given in Table 1. In addition to routine haematological investigations, red cell mass was measured using $^{51}$Cr-labelled red cells and plasma volume by $^{[125]}$human serum albumin. Liver function tests, including bromsulphthalein excretion, were performed together with percutaneous liver biopsy.

**Haemodynamic methods**

Details of the technique for measuring spleen blood flow (ml 100 g$^{-1}$ min$^{-1}$) are given elsewhere (Williams et al., 1968). $^{133}$Xenon dissolved in saline was injected through a catheter positioned in the splenic artery and inserted by percutaneous femoral artery puncture. After the flow measurement, a selective coeliac arteriogram was performed including films of the late venous filling phase to show the portal vein and any collateral vessels present (Kree1 & Williams, 1964). From the area of spleen on one of these radiographs the spleen weight was determined from the regression equation:

$$\log_{10} \text{spleen weight (g)} = 0.0027 \text{area (cm}^2) + 2.36$$

(Blendis et al., 1969c) and the total spleen blood flow calculated. In patients who were later treated by splenectomy there was good agreement between the calculated spleen weight and that determined at operation.

Estimated hepatic blood flow was determined by measuring the hepatic extraction of a constant intravenous infusion of indocyanine green (Caesar et al., 1961). Splenic artery, intrasplenic, wedged and free hepatic vein, right atrial and inferior vena caval pressures were also recorded and the following resistances calculated:
Post-sinusoidal resistance (dynes sec cm\(^{-5}\))

\[
\text{Post-sinusoidal resistance (dynes sec cm}^{-5} = \frac{(\text{Wedged hepatic vein} - \text{Free hepatic vein pressure}) \text{ mmHg} \times 80}{\text{Estimated hepatic blood flow (l/min)}}
\]

Splenic resistance (dynes sec cm\(^{-5}\))

\[
\text{Splenic resistance (dynes sec cm}^{-5} = \frac{(\text{Splenic artery} - \text{Intrasplenic pressure}) \text{ mmHg} \times 80}{\text{Total spleen blood flow (ml/min)}}
\]

The cardiac output was estimated by the Fick principle using pulmonary and peripheral arterial samples and the measured oxygen consumption except in three patients in whom it was determined from a dye dilution curve of indocyanine green.

**RESULTS**

**Blood dyscrasia and diseases involving the reticulo-endothelial system**

The results of haematological investigations and liver function tests are given in Table 1. Three patients had thrombocytopenia with a leucopenia and five other patients thrombocytopenia alone. The blood volumes were increased more than 80 ml/kg, the upper limit of the normal range, in thirteen out of seventeen patients investigated. This increase in blood volume was due to a proportionally greater increase in the plasma volume than in the red cell mass, and resulted in a haemodilutional anaemia in fourteen patients with haemoglobin concentrations of 7.0-10.9 g/100 ml. Three patients had elevated serum alkaline phosphatase and transaminase levels which in two cases (Nos. 3 and 9) were associated with portal tract fibrosis. In case 3 there was also a dense cellular infiltration, whilst in the third patient (case 7) there was no marked histological abnormality (Table 1).

**Splenic and hepatic haemodynamics**

The intrasplenic pressure was greater than 13 mmHg, the upper limit of the normal range, in thirteen out of the twenty patients (Table 2). The height of the intrasplenic pressure was closely correlated with the increase in spleen size \((r = +0.72, P < 0.01)\). In seven patients the pressure was more than 20 mmHg and three of these had either abnormal collateral vessels around the splenic capsule or left gastric collaterals, visible on the venous phase of the coeliac arteriogram. One of these, a patient with Felty's syndrome and an intrasplenic pressure of 27 mmHg, also showed oesophageal varices on barium swallow. The other two patients were suffering from chronic leukaemia. None of the patients gave a history of gastrointestinal bleeding and in all patients in the group both splenic and portal veins were shown to be patent.

Spleen blood flow was reduced below 60 ml 100 g\(^{-1}\) min\(^{-1}\), the lower limit of the normal range, in ten patients. An inverse relationship \((r = -0.47, P < 0.05)\) was found between this measurement of spleen blood flow and spleen size, the patients with the largest spleens having the smallest flows per 100 g of tissue. However, the total spleen blood flows were increased in all but one of these patients with values of up to 1550 ml/min. Four patients had flows of 1000 ml/min or more as compared with the upper limit of normal of 300 ml/min.

Splenic resistance was decreased in all but two patients (Table 2). One of these was the patient with normal total flow and in the other the spleen blood flow was only slightly increased. The fall in resistance was correlated with the increase in spleen size and spleen blood flow as illustrated in Fig. 1.

Liver blood flow was increased above 810 ml min\(^{-1}\) m\(^{-2}\), the upper limit of normal for this
# Table 1. Clinical and haematological data together with liver function and histology

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<th>Diagnosis</th>
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<th>Platelets (x $10^3/mm^3$)</th>
<th>Ref. cell mass volume (ml/kg)</th>
<th>Plasma Alkaline trans. phosphatase (KAu/100 ml)</th>
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**Normal values**

- Hb: > 11.5
- WBC: 3–11
- Platelets: 100–500
- Ref. cell mass volume: 22–34
- Plasma Alkaline trans. phosphatase: 34–48
- Aspartate trans.: 3–13
- Portal tract fibrosis: < 40
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<th>Right atrial pressure (mmHg)</th>
<th>Cardiac index (l/min/m²)</th>
<th>Blood flow (l/min)</th>
<th>Mean pressure (mmHg)</th>
<th>Pulp pressure (mmHg)</th>
<th>Total resistance (dynes sec cm⁻²)</th>
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<th>Free sinusoidal pressure (mmHg)</th>
<th>Wedged vein pressure (mmHg)</th>
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**Normal values**

- Cardiac index: 2.5-4.5 l/min/m²
- Blood flow: 0.3-0.8 l/min
- Mean pressure: 2-8 mmHg
- Pulp pressure: 5-12 mmHg
- Cutaneous pressure: 2-8 mmHg
- Total flow: 120-200 ml/min
- Blood flow: 100-300 ml/min
- Mean pressure: 22-65 mmHg
- Pulp pressure: 100-300 mmHg
- Total flow: 22-65 ml/min

*Spleen weight measured at splenectomy.*
technique (Levy et al., 1962) in thirteen of seventeen patients in whom it was measured. Values ranged up to 2615 ml min\(^{-1}\) m\(^{-2}\) and in eight patients were more than 1000 ml min\(^{-1}\) m\(^{-2}\) (Table 2).

The cardiac index was measured in sixteen patients and was moderately increased in four (Table 2). These patients had a marked haemodilution anaemia, considerable splenomegaly, as well as high spleen and liver blood flows (Fig. 2). One patient with an increased cardiac index of 6.25 l min\(^{-1}\) m\(^{-2}\) had a slightly raised right atrial pressure of 8 mmHg. The percentage of cardiac output passing through the liver was greater than the normal 30% in eight patients and in three patients it was 50% or more.

The wedged hepatic vein pressure was measured in sixteen patients including eleven of the thirteen with a raised intrasplenic pressure. It was elevated, at 12 mmHg or more, in eight patients. In one patient this was a reflection of a raised intra-abdominal pressure, the inferior vena caval pressure being 12 mmHg and free hepatic vein pressure 13 mmHg. In two others, including the patient with Felty's syndrome (case 9) and one with Gaucher's disease (case 11), the raised wedged hepatic vein pressure was associated with an increased post-sinusoidal resistance (Fig. 2). The cause of this was uncertain. Serum alkaline phosphatase and transaminase levels were increased in the first patient and in the second the bromsulphthalein retention at 30 min was increased at 18.5%. Histological examination of liver biopsies revealed portal tract fibrosis in both patients. In the patient with Felty's syndrome there was considerable variation in cell size giving rise to an appearance of 'nodule' formation on the haemotoxylin–eosin preparation, and in the patient with Gaucher's disease disorganization of the
lobular architecture with lipid infiltration of hepatocytes. In neither case did the reticulin preparations show evidence of nodule formation and liver surfaces appeared normal at the time of splenectomy. In the remaining five patients the raised wedged hepatic vein pressure was related to the increase in liver blood flow and the calculated post-sinusoidal resistance was normal (Fig. 2).

A difference of more than 5 mmHg between the intrasplenic pressure and the wedged hepatic pressure has previously been defined as an increased pre-sinusoidal resistance (Williams et al., 1966). This was present in nine of the sixteen patients in whom both pressures were measured (Fig. 3). These included the patients with the higher intrasplenic pressures and raised wedged pressures and one of the two patients (case 9) with an increased post-sinusoidal resistance referred to above. All nine patients had considerable splenomegaly, with marked increases in total spleen and liver blood flows. The mean liver blood flow was 1-40 1 min\(^{-1}\) m\(^{-2}\) compared to 0.92 1 min\(^{-1}\) m\(^{-2}\) in the seven patients with normal pre-sinusoidal resistance, although the difference of the means was not statistically significant. There was no difference in the incidence of portal tract fibrosis or of cellular infiltration in the sinusoids or portal tracts between the two groups.

**Arteriographic findings**

The width of coeliac axis, splenic and hepatic arteries was compared with those of a control group (Blendis et al., 1969b). The coeliac axis was dilated in six patients, with a diameter greater than 1·1 cm, the upper limit of the normal range. The width of the hepatic artery (mean 0·75, range 0·5–1·1 cm) was not significantly different from that of the controls, but the splenic artery was considerably dilated. It was greater than 0·8 cm in diameter, the upper limit of the normal range, in sixteen out of nineteen patients, the maximum being 1·4 cm. The artery was also tortuous and greater than 25 cm in length, the upper limit of normal, in six patients.
There was a significant correlation between the width of the splenic artery and the total spleen blood flow \((r = +0.75, P<0.001)\).

**Comparison with idiopathic splenomegaly and cirrhosis**

The range of spleen sizes in the present series was similar to that in patients with tropical splenomegaly, the mean value in the latter group being slightly greater (Fig. 4). The intrasplenic pressure was raised less frequently in blood dyscrasia, thirteen of twenty patients, compared to all fifteen in the tropical splenomegaly group and the mean value was lower, 16.4 mmHg compared to 22.6 mmHg. In both series the incidence of a collateral circulation seen on venography, three of twenty and two of fifteen, was equally low. Spleen blood flow, in ml 100 g\(^{-1}\) min\(^{-1}\), was equally reduced and showed a similar inverse relationship to the weight of the spleen so that the mean total spleen blood flows and range of values was very similar (Fig. 4). Despite the differences in portal pressure the splenic resistances were comparable in the two groups (Fig. 1). The increases in liver blood flow in the present series were of similar magnitude with a mean of 1216 ml min\(^{-1}\) m\(^{-2}\) compared to 1280 ml min\(^{-1}\) m\(^{-2}\) in the tropical splenomegaly patients. These increases were associated with the same percentage of patients with a raised pre-sinusoidal resistance, nine of sixteen and six of eleven patients respectively. The only major difference between the two groups was the increase in post-sinusoidal resistance seen in two of the present patients which was not found in any of the tropical splenomegaly patients.

The mean spleen weight in the twenty-two cirrhotic patients was considerably lower than that of the other two groups, and in fourteen patients the weight was either within or just
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outside the normal limit. The mean spleen blood flow in ml 100 g⁻¹ min⁻¹ was normal in the cirrhotic group in contrast to the present patients and those with tropical splenomegaly and there was no inverse relationship with spleen size. The cirrhotic patients with the largest spleens had a normal spleen blood flow per 100 g of tissue. This resulted in the total spleen blood flow (ml/min) in the cirrhotic patients, especially in the three patients with massive splenomegaly, being higher than in patients with blood dyscrasia (Fig. 4). Hepatic haemodynamics were not studied in this group of patients but in five patients the intrasplenic pressure was measured and found to be raised, with values of 17–36 mmHg.

Nine cirrhotic patients were studied only after a portacaval anastomosis (Williams et al., 1968). In seven of these patients the spleen weight was within normal limits. Spleen blood flow

![Fig. 4. Comparison of the spleen size and blood flow in patients of the present series with those found in tropical splenomegaly and cirrhosis. The cross-hatched areas indicate the normal ranges and the vertical lines the mean values.](image)

in ml 100 g⁻¹ min⁻¹ was normal, ranging from 80 to 140 ml 100 g⁻¹ min⁻¹; in general the values lay in the upper half of the normal range. In the whole group there was no relationship to spleen size. Furthermore in the seven patients with a normal spleen weight total spleen blood flow (ml/min) was within normal limits and in the others with persistent splenomegaly the flow was moderately increased.

In one cirrhotic patient, studied before and 3 months after a shunt operation, the estimated spleen weight was reduced from 417 to 250 g. This was associated with an increase in spleen blood flow in ml 100 g⁻¹ min⁻¹ from 71 to 113 and the calculated pre- and post-operative total spleen blood flows were 296 and 284 ml/min respectively.

**DISCUSSION**

The incidence of portal hypertension in the present series of patients with blood dyscrasia was higher than previous reports have suggested since a raised intrasplenic pressure was present
in over half the patients, and in a third there was considerable portal hypertension with pressures greater than 20 mmHg. However, only three patients had demonstrable portal systemic collaterals, and only one had oesophageal varices. From the number of reported cases in the literature, portal hypertension appears to be more common in the myeloproliferative disorders (Shaldon & Sherlock, 1962; Rosenbaum et al., 1966) and in chronic leukaemia (Paraf et al., 1955) than in Hodgkin's disease (Lima et al., 1962) and Gaucher's disease (Javett, Kew & Litnaitsky, 1966). However, this may be accounted for by the added factor of a portal vein thrombosis which may occur especially in the myeloproliferative disorders though it was not found in any of the patients in this series.

The degree of portal hypertension in these patients appeared to be closely related to the extent of splenic enlargement and to the accompanying increase in spleen blood flow. There was a corresponding increase in liver blood flow, and elevation of the wedged hepatic venous pressure, although in two patients the increase in wedged pressure was relatively greater due to an increased post-sinusoidal resistance. In nine out of sixteen patients the increased liver blood flow was associated with an increased pre-sinusoidal resistance. The main difference between these nine patients and the seven patients with a normal pre-sinusoidal resistance was the magnitude of the blood flow since liver biopsy showed portal tract fibrosis and cellular infiltration in some patients of both groups. Thus the cause of this increased resistance may be the combination of a greatly increased blood flow through the liver with a limitation in hepatic vascular distensibility due to the surrounding fibrosis and cellular infiltration.

Although the present series included patients with different conditions and varied splenic pathology, the changes in splanchnic haemodynamics followed a similar pattern and were very similar to those found in idiopathic tropical splenomegaly (Williams et al., 1966). These included the effect of splenic enlargement on lowering spleen blood flow per 100 g of tissue and on increasing total spleen blood flow (with a decrease in splenic resistance) and liver blood flow together with, in some patients, an increase in the pre-sinusoidal resistance. In general, portal hypertension tended to be more frequent in the tropical splenomegaly patients but the series are relatively small and too many conclusions should not be drawn.

In contrast with these two groups, splenic enlargement in cirrhosis is not consistently associated with a decrease in spleen blood flow per 100 g of tissue, so that cirrhotic patients with considerably enlarged spleens have relatively higher spleen blood flows. This is consistent with the cirrhotic spleens having proportionally wider splenic arteries, since this is related to blood flow, and the splenic pulp appearing to be more vascular with prominent dilated peripheral vessels (Blendis et al., 1969b). With this increase in total spleen blood flow in cirrhosis splenic resistance was reduced similarly to the other two groups. This may be related to the higher portal pressure which occurs generally in cirrhosis and the prominent congestive changes of portal hypertension seen on histological examination of the spleen (McMichael, 1934; Moschcowitz, 1948). An increased spleen blood flow with a corresponding increase in liver blood may account for the raised pre-sinusoidal resistance seen in some patients with cirrhosis (Levey et al., 1962). With the development of regeneration nodules in the liver portal hypertension is mainly due to the raised post-sinusoidal resistance resulting in extensive collateral circulation and a drop in liver blood flow. This was not found in any of the patients with tropical splenomegaly and although two patients with blood dyscrasias had an increased post-sinusoidal resistance neither patient had evidence of regeneration nodules.

In cirrhosis, in contrast to blood dyscrasia and tropical splenomegaly, there is also a general-
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ized hyperdynamic state associated with the increased cardiac output (Murray, Dawson & Sherlock, 1958) with an increased blood flow through skin and muscle (Kontos et al., 1964) and brain (Polli et al., 1967). Except in a few patients with a severe haemodilution anaemia and markedly raised spleen blood flow, an increased cardiac output was not found in the patients with blood disease and tropical splenomegaly. Blood is diverted through the spleen and liver, splanchnic flow accounting for an increased percentage of the normal cardiac output.

Another effect of splenomegaly in these patients was an increase in blood volume with a proportionally greater increase in plasma volume than red cell mass resulting in a haemodilutional anaemia. This has also been observed in idiopathic tropical splenomegaly and in cirrhosis (Richmond et al., 1967; Kimber et al., 1965). In blood dyscrasias (Bowldeker, 1963; Blendis, Clarke & Williams, 1969a) and tropical splenomegaly (Pryor, 1967) splenectomy results in a return of the blood volume to normal, although in cirrhosis it is only partially reduced (McFadzean & Todd, 1967). It is of interest that Lieberman & Reynolds (1967) found a correlation between the increase in plasma volume and wedged hepatic venous pressure in cirrhosis, and in the present patients with blood dyscrasia we have similarly found significant correlations of both intrasplenic and wedged pressures with plasma volume.

Fifteen of the patients received treatment for their primary medical condition. Five were treated medically with cytotoxic drugs, nine by splenectomy, and one by irradiation to the spleen. Splenectomy or shrinkage of the spleen by chemotherapy or irradiation should result in a fall in liver blood flow and regression of the portal hypertension, but this was not confirmed for various reasons, in any of the patients in the present series.

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REFERENCES


