ANAESTHETIC AND SURGICAL CONSIDERATIONS IN PARTIAL HEPATECTOMY

JOHN I. DAVIES, M.D., F.R.C.P.(C), AND ABRAHAM KAPLAN, M.D.*

IN NORTH AMERICA the indications for partial hepatectomy are relatively uncommon, being confined to trauma and neoplastic disease. It is unusual to find secondary neoplastic hepatic deposits singly or limited to an area where partial hepatectomy would be indicated. When they are present the colon is the usual primary site. However, in some parts of Africa and the Far East primary carcinoma is relatively common; it is the commonest of all forms of carcinoma in Java.[1] In Japan, carcinoma of the stomach with a single hepatic metastasis is said to be frequently seen.[2]

The first reported case of surgical repair in liver injury was by Bruns[3] in 1870. The known advances in anaesthesia since then and the impact of muscle relaxants during abdominal surgery are well recognized. During the past 20 years surgeons have shown an increasing interest in liver surgery. This is attributed to a better understanding of hepatic physiology and haemodynamics and some refinement of surgical technique. However, control of bleeding is still the single most important problem confronting the surgeon.

We were interested in experimental liver resection using controlled systemic hypotension and reduced portal flow employing trimethaphan (Arfonad®) and vasopressin (Pitressin®); later we became concerned with various problems arising from our results. It was felt advisable to determine the effects of each drug used alone and to compare them with the results obtained using both drugs. It would be of further interest to determine the hepatic haemodynamic effects of these agents.

METHOD

The method was based on the work of Kaplan *et al.*[4] Ten control and thirty experimental mongrel dogs weighing an average of 18.4 kg. were used. Base line liver function studies consisting of alkaline phosphatase, BSP, SGOT, serum bilirubin, serum albumin, and total protein tests were carried out, and these parameters were again measured twice weekly for four weeks after hepatic resection. Haematocrit and blood volumes were checked before resection and every other day afterwards for one month. Sodium pentobarbital 25 mg./kg. was used as the sole anaesthetic agent, and was repeated in small doses if necessary. Endotracheal intubation and a Harvard positive pressure respirator delivering room air were used in all experiments. Slight hyperventilation was employed using the standard ventilation volumes of Hemmingway.[5]

Central venous pressure was measured by a polyethylene catheter introduced through the jugular vein. Systemic blood pressure was continuously measured in

*Department of Surgery, Veterans Administration Hospital, Kansas City, Missouri, and Departments of Anesthesia and Surgery, University of Kansas School of Medicine.

the aorta at the level of the coeliac axis by a catheter introduced through the femoral artery.

The hepatic vein pressure was measured by a catheter introduced through the femoral vein and placed by manual manipulation after laparotomy was performed. The catheter at the coeliac axis and the one at the hepatic veins were used to draw samples of blood before and after induction of hypotension to determine the A-V oxygen difference across the liver substance. Portal pressures were similarly measured by means of an 18-gauge Intracath® introduced through a small purse string into the superior mesenteric vein. The tip of the catheter was placed manually in the main trunk of the portal vein just proximal to the bifurcation. All pressures were calibrated and amplified using Statham Strain gauges and registered on a multichannel recorder (Electronics for Medicine). Hepatic artery and portal vein blood flows were monitored using electromagnetic square-wave probes (Carolina Medical Electronics) which were very carefully selected according to the individual vessel calibre. Probes were connected to a flowmeter for direct measurement of flow and recorded on the polygraph.

A liver biopsy was taken before induction of hypotension, and comparative histologic studies were made of the sections taken before and after drug administration. All above mentioned parameters were recorded before, during, and after the intravenous administration of trimethaphan and vasopressin. Trimethaphan was administered slowly in divided doses until systemic blood pressure was reduced to a mean of 60 mm. Hg. Vasopressin was then given in amounts of 10 units and if necessary repeated until an appreciable reduction of portal blood flow was detected. A liver resection was then performed, disregarding anatomical landmarks. Vertical mattress sutures of 2–0 chromic catgut were placed along the line of resection before resection was accomplished. An average of 35 per cent of the liver substance was removed. The control group was handled similarly except that no drug was given and the animals were sacrificed one day later.

In the haemodynamic studies 10 microcuries of I^{131} (RISA) was injected into the splenic vein and changes noted in radioactivity between the hepatic vein and aortic blood.

Results

Of the ten control animals, four died within 24 hours, and autopsy showed an average of 275 ml. of blood in the abdominal cavity. The six surviving dogs showed a decrease in blood volume averaging 42 per cent and were sacrificed.

Of the 30 experimental animals the reduction in blood volume averaged 7 per cent after 24 hours (Fig. 1). Three dogs died of respiratory complications within 48 hours but none showed intra-abdominal bleeding at autopsy.

Arterial oxygen saturation of 97 per cent did not show any significant change before and after induction of hypotension, but the venous saturation across the liver fell from an average of 79 per cent to an average of 57 per cent (measured in the hepatic vein). A slight increase in blood pH from 7.50 to 7.52 was observed, probably caused by the slight hyperventilation, confirmed by a reduction in

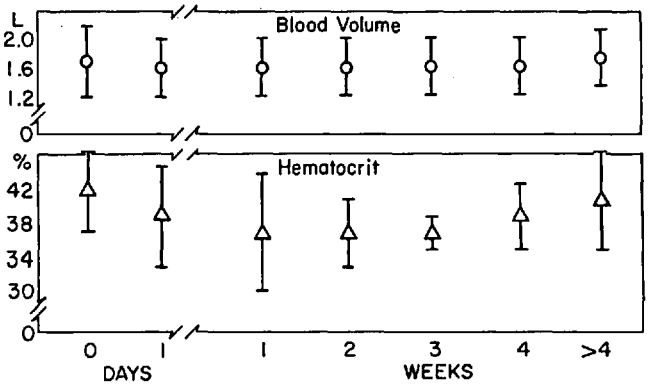

FIGURE 1. Blood volume and haematocrit readings following liver resection in dogs which received trimethaphan and vasopressin.

arterial P_{CO_2} from 46 to 39 (average in 10 dogs). Dogs were placed on the ventilator for ten minutes before any drug was given. The liver resection was accomplished with minimal blood loss and all recorded haemodynamic measurements were consistently back to normal values in 45 minutes. The postoperative liver studies showed no appreciable changes. Comparative histological studies revealed no pathological changes following the use of controlled hypotension. The radioactive studies were performed on 75 dogs as follows: no drug–8 dogs; trimethaphan–40 dogs hypotensive for 2, 15, 30, and 45 minutes (10 dogs in each subgroup); vasopressin–12 dogs; trimethaphan and vasopressin–15 dogs.

In these studies four patterns were seen and are shown in Figure 2. The

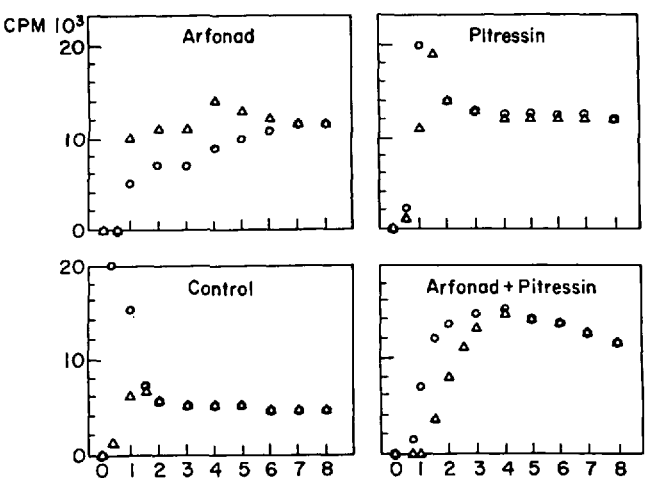

FIGURE 2. Comparative isotopic studies depicting radioactivity concentration in blood samples taken from femoral (△) and hepatic (○) veins.

average dose of trimethaphan for 45 minutes of hypotension was 1.10 mg. The following values are averages and flows in ml./min. We found a consistent reduction in hepatic artery flow following a fairly linear relationship to the mean systemic blood pressure. The hepatic artery showed a drop from 162 ml. to 71 ml. The aortic pressure dropped from 142/100 to 65/48. A mean pressure of 60 mm. Hg. was maintained whenever possible. A reduction in portal vein flow from 208 ml. to 84 ml. was observed. The portal vein pressure rose immediately from 5.1 mm. Hg. to 10.2 mm. Hg. and gradually fell over 45 minutes to a pressure of 7.2 mm. Hg. It was noticed that following trimethaphan the liver became dusky or "plum coloured." These results are shown in Figure 3. Electrocardiogram showed only bradycardia, low takeoff ST segment, and occasional T wave inversion related to mean aortic pressure.

In the series of 12 dogs given 12.5 units of vasopressin, four showed marked but transient EKG changes and all showed a slight transient increase in systemic blood pressure, the hepatic artery flow again being closely related to the systemic blood pressure (Fig. 4). The portal vein pressure decreased from 5.1 to 1.35 mm. Hg. and the portal flow decreased from 212 to 64 ml. The appearance of the liver was bright pink throughout.

In 45 dogs the average dose of trimethaphan was 1.25 mg. Vasopressin was given at an average dose of 12.5 units. The systemic pressure dropped from 144/104 to 65/48. The hepatic artery flow decreased from 219 ml. to 68 ml. The

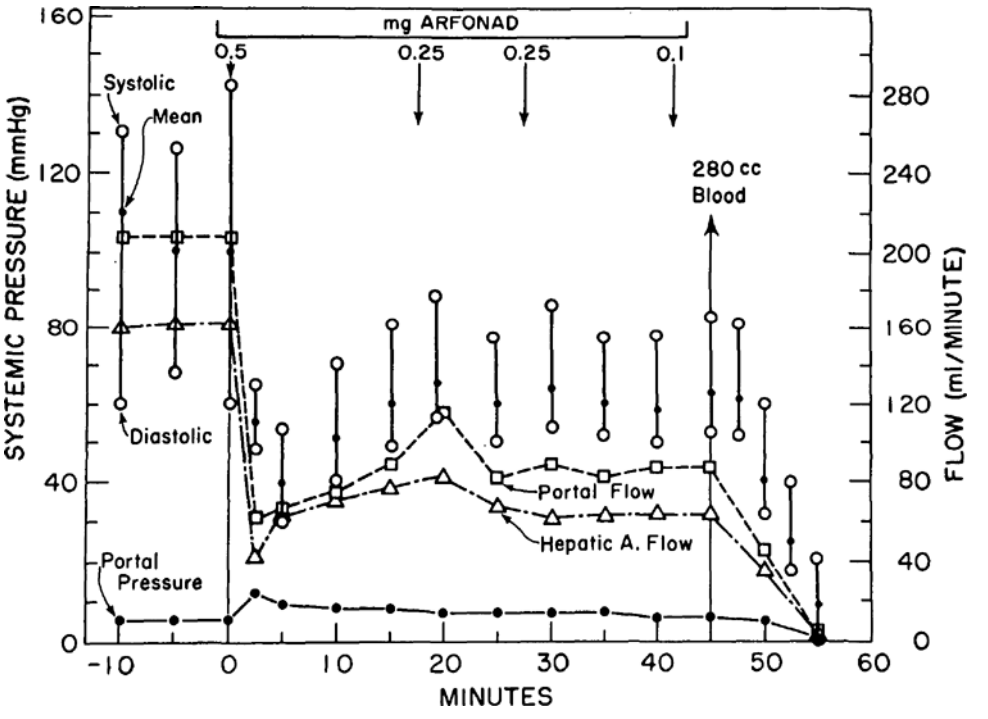

FIGURE 3. Response of systemic blood pressure (systolic, diastolic, and mean), portal vein flow, hepatic artery flow, and portal vein pressure before and during controlled hypotension; and effects of haemorrhage.

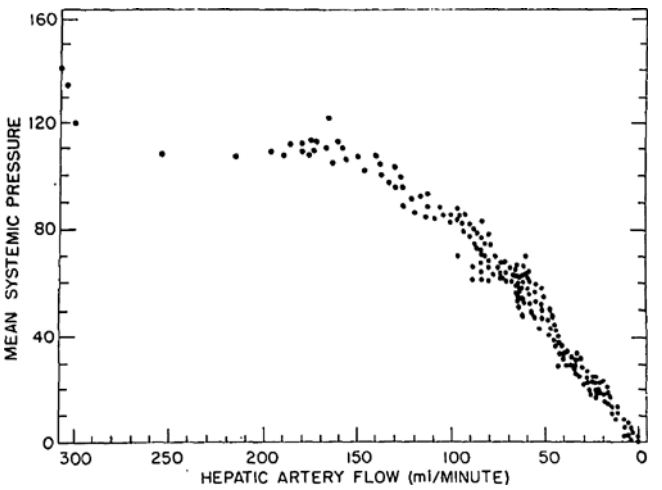

FIGURE 4. Relation between mean systemic blood pressure and hepatic artery flow in 25 dogs selected at random.

portal vein flow dropped from 183 ml. to 56 ml. and the portal pressures fell from 5.3 to 1.4 mm. Hg. following vasopressin. Following trimethaphan it rose to 10.2 but the liver remained normal in colour and appearance.

DISCUSSION

The haemodynamics of the liver are complicated and the usual accepted vascular anatomical arrangement is shown in Figure 5. The RISA studies show that shunts exist. It would seem from these experiments that the portal and hepatic systems function with some degree of autonomy, and that trimethaphan produces its effects mainly on the systemic arterial circulation while vasopressin affects primarily the portal system. When a combination of the two drugs was used the observed pattern closely approached that seen in the control animals. Low levels of arterial blood pressure are known to be harmful when accompanied by either vasoconstriction or hypovolaemia, but presently there is much evidence, both experimental and clinical, that in normal patients carefully controlled hypotension is not necessarily a harmful technique.[6–10] In the case of the liver, the relatively high oxygen saturation in the hepatic vein (range 79 to 57%) would seem to protect this organ to some extent from the deleterious effects which may accompany hypotension and hypoxia.

Although trimethaphan has been used widely in clinical anaesthesia with dosage, indications, contraindication, advantages, and disadvantage well established,[11–13] this drug produces different effects in dogs, which are unusually sensitive to it. Randall *et al.*[14] found the LD_{50} to be .75 mg./kg. in dogs compared with 38 mg./kg. in mice and 78 mg./kg. in monkeys. This was attributed to histamine release. Page confirmed this sensitivity and attributed the effects primarily to direct peripheral vasodilation, concluding that ganglion sympathetic blockade and histamine release to play a minor part.[15] Using trimethaphan in 92 dogs we found 85 to be predictably sensitive, two to be resistant to large doses,

and five to be unusually sensitive, 0.5 mg. producing profound and sustained hypotension which did not respond to antihistamine drugs or various peripherally acting vasoconstrictors, but did respond to either isoproterenol or epinephrine, suggesting that a direct myocardial effect may have been present.

Vasopressin has been used to reduce portal pressure in the treatment of bleeding oesophageal varices.[16–20] Estimates of its efficiency vary from 25 to 40 per cent success, with an additional 16 per cent success when combined with oesophageal tamponade. Dosage has varied from 20 to 50 units given by intravenous drip over periods ranging from 5 to 20 minutes. Little hypertension was noted, but the danger of coronary artery constriction is constant. We have seen coronary constriction lead to myocardial infarction and death in one patient treated by vasopressin.

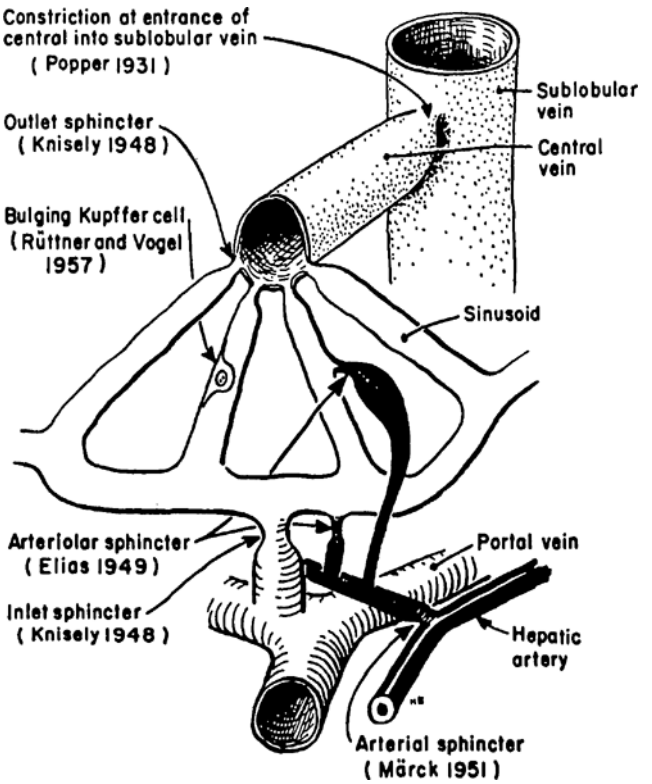

FIGURE 5. Mechanisms that control the flow of blood through the liver. (From H. Elias and J. E. Pauly, Human Microanatomy (Philadelphia: F. A. Davis), reproduced from Gastroenterology, by Henry L. Bockus, vol. III.)

CLINICAL APPLICATION

Extrapolation to human surgery of these findings in dogs concerning the response to trimethaphan is obviously unsound and misleading. However, using trimethaphan for carefully controlled hypotension during the limited time needed

for partial hepatectomy would be beneficial to the patient in reducing blood loss and facilitating and shortening the surgical procedure.

The use of vasopressin would be inadvisable in the elderly and in patients with known cardiovascular disease. However, 20 units of vasopressin administered over 20 minutes might be beneficial to an otherwise fit and healthy young adult with traumatic rupture of the liver in spite of possible cardiovascular effects. Other polypeptides have been tried as an alternative. Hypertensin® (Angiotesin II) produces no direct change in hepatic haemodynamics. Recently Tsarasos *et al.*[21] have reported favourably on 2-phenylalanine-8-lysine vasopressin (Octapressin). Hunter and Gordon in laboratory and clinical studies found Octapressin innocuous to the cardiovascular system.[22]

We have used trimethaphan alone in partial hepatectomy in one elderly patient suffering from arteriosclerotic heart disease and carcinoma of the colon with a large solitary metastasis in the liver. Resection of the liver lesion was accomplished with negligible blood loss in 12 minutes. The systolic blood pressure was maintained between 80 and 86 for 10 minutes. Recovery was uneventful.

By comparison with known human values on a weight basis, there is good correlation in normal blood volumes and total liver flow of about 1.25 to 1.5 L./min. (roughly 25% of the cardiac output).[23] Price and his colleagues, using the indocyanine green method, found similar values in conscious volunteers before induction of halothane or cyclopropane anesthesia.[24,25]

However, it is important to differentiate between the hepatic artery and portal vein contribution to the total flow. This has been done by Galindo[26,27] in dogs, using electromagnetic flowmeters, with very interesting results under many varying conditions, but not under profound hypotension.

The necessity is confirmed of maintaining a normal blood volume when trimethaphan is used.

Conclusion

It appears that hepatic artery flow is dependent on systemic blood pressure and that portal vein flow is dependent on the splanchnic circulation. The liver is capable of some degree of homeostasis depending on the presence of various shunts and sphincter mechanisms. At present our experimental work would seem to indicate that a correlation of portal vein pressure and these shunts may be of importance.

Since severe bleeding is the single most troublesome technical difficulty encountered, the technique here described of controlled systemic hypotension and reduction of both systemic and portal blood flow would seem an acceptable method for patients in whom the urgency of circumstances would hardly justify a more prolonged surgical procedure.

According to our isotopic studies it is suggested that derangement of the hepatic artery flow is more critical than derangements affecting the portal system. It is also suggested that intrahepatic blood flow homeostasis is perhaps more dependent on regulatory mechanism of the hepatic artery vasculature than the portal vein system.

It appears that dogs can withstand hypotension for 20 minutes with resection of 35 per cent of liver substance with minimal after-effects.

Summary

A new technique for reducing bleeding during partial hepatectomy has been investigated in dogs. It consists of producing systemic hypotension using trimethaphan alone, and in combination with vasopressin. Hypotension of 20 minutes and resection of 35 per cent of liver substance produced minimal bleeding and insignificant effects on liver function. Further studies are in progress to determine the effects on liver function of hypotension up to 45 minutes in duration and to learn the significance of liver shunts and sphincter mechanisms. Preliminary results are briefly discussed. The hepatic artery flow is dependent on mean aortic pressure. The clinical usefulness of this technique is discussed.

Résumé

Nous avons étudié une nouvelle technique pour réduire les pertes sanguines au cours de l'hépatectomie partielle. Nous avons examiné sur des chiens l'effet de l'hypotension systémique en employant seul le trimethaphan et en l'associant à la vasopressine. Une hypotension d'une durée de 20 minutes et une amputation de 35 pour cent de la substance hépatique n'ont produit que des pertes sanguines minimes et des effets négligeables sur la fonction hépatique.

D'autres études sont actuellement en cours pour préciser les effets sur la fonction hépatique d'une hypotension se prolongeant jusqu'a 45 minutes ainsi que la signification des dérivations hépatiques et des mécanismes des sphincters. Nous avons brièvement discuté les résultats préléminaires. Le débit de l'artère hépatique est régi par la pression moyenne dans l'aorte. Nous avons parlé de l'utilité clinique de cette technique.

Acknowledgments

The authors are indebted to Mr. Shannon Lucas and Mr. George Buckaloo for their technical assistance; to the medical illustration department, Mrs. Kay Wahl and Mr. Harold Bowen; and to Mrs. N. Rubelee and Mrs. J. Peeples for their devoted efforts in preparing the manuscript.

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