

A MULTIPLE CATHETER
TECHNIQUE FOR STUDIES OF
HEPATIC METABOLISM AND
BLOOD FLOW IN DOGS WITH
PORTACAVAL TRANSPOSITION

STUDIES ON HEPATIC BLOOD
FLOW AND THE RATE OF
BROMSULPHALEIN CLEARANCE
IN DOGS WITH PORTACAVAL
TRANSPOSITION

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A multiple catheter technique for studies of hepatic metabolism and blood flow in dogs with portacaval transposition

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Precise in vivo studies of hepatic metabolism have been difficult to obtain under ideal conditions. Minute to minute evaluation of hepatic function requires knowledge of hepatic blood flow as well as analysis of metabolites entering and leaving the liver via relatively inaccessible vascular channels.

The purpose of this report is to describe a method by which simultaneous transhepatic metabolic gradients and blood flow can be determined in awake, unanesthetized dogs, with the use of simple catheterization techniques. The method appears to be applicable to a wide range of problems involving liver metabolism. Concomitant gradients can be obtained across other capillary beds including the nonhepatic splanchnic area and hindquarters.

METHOD

Preliminary surgical preparation. Portacaval transposition is performed from 2 to 6 months before testing. The operation is

performed under hypothermia* to protect the bowel from the effect of acute portal obstruction. At the same stage, all tributaries to the inferior vena cava from the inguinal ligaments to the diaphragm are divided, with the exception of the renal veins.⁶ After operation, the animals resume a normal kennel routine. After several months, they are trained to lie quietly on a table.

Catheterization. All catheters are inserted under local anesthesia through peripheral cut-downs (Fig. 1) and guided into position with fluoroscopic control. Side branches are used, and the main vessels are preserved. No. 8 or 10 Goodale-Lubin and straight cardiac catheters† are used for the hepatic vein and distal portal vein, respectively. Polyethylene (PE 190), opacified with 50 per cent Hypaque‡ solution, is used for the other catheters.

Cannulation of the hepatic vein¹⁴ is done with the dog in the lateral position. The

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*Described in addendum to paper by Starzl, Butz, and Munger.¹²

†American Cytoscope Makers, Inc., Pelham, N. Y.

‡Winthrop Laboratories, New York, N. Y.

Goodale-Lubin catheter which has a curved tip is passed through the superior vena cava and right atrium into the inferior vena cava. The angled tip is then directed to the left. It will pass into the left main hepatic vein for 2 to 4 inches. In the lateral position, the catheter appears to be running anteriorly (Fig. 2, A). When the dog is rolled on its back, the catheter can be seen in the left portion of the liver (Fig. 2, B). The catheter is checked for ease of blood withdrawal. If this is difficult, the catheter is pulled out cautiously until withdrawal is easy. Its position is then rechecked. No branch except the left main hepatic vein is considered by us to be suitable for sampling.

The splanchnic catheter is passed from the other external jugular vein through the right atrium, venae cavae, and anastomosis into the distal portal vein (Fig. 1). Its fluoroscopic configuration is a gentle curve in the lateral position (Fig. 2).

The venous inflow to the liver is sampled by a catheter passed from a side branch of the femoral vein, through the vena cava and anastomosis, into the hilum of the liver (Fig. 1). The catheter will usually be in the correct position if passed blindly until resistance is met, but this is easily confirmed fluoroscopically (Fig. 2).

The arterial catheter is similarly passed through a side branch into the iliac artery or aorta (Fig. 1). Its exact position is not important so long as free pulsatile flow can be obtained, but our preference in the matter is to place it in the midabdominal aorta (Fig. 2).

Injection catheters are placed in suitable arm veins (Fig. 1) and in the lower vena cava (Fig. 1). As long as the caval catheter is well above the inguinal ligaments, injected drugs or dyes pass exclusively through the liver (Fig. 3).

Measurement of hepatic plasma flow. Hepatic plasma flow is measured by the Bromsulphalein (BSP) method described by Bradley and his associates,¹ using the Shoemaker⁸ correction for hemolysis. The dye is delivered into a forelimb vein by a constant infusion pump (Fig. 1). Hindlimb infusion

could conceivably distort results because this would involve infusing BSP into and sampling it from the same vessel. With hepatic plasma flow, and the hematocrit, hepatic blood flow can be computed.

Samples. Time-integrated aliquots of blood are simultaneously drawn from the various sampling catheters as desired. Before definitive collection, catheter "dead space," which is about 1 c.c., is cleaned by preliminary removal of 2 or 3 c.c. of blood. This blood is subsequently returned to the animal.

Replacement of the blood loss from the actual samples has been done in two ways. It can be replaced by small transfusions after each withdrawal, or with one large transfusion given several hours in advance of the experiment. If the blood loss from sampling is not excessive, the pretransfusion method has seemed to provide more consistent results.

The quantity of blood per sample and

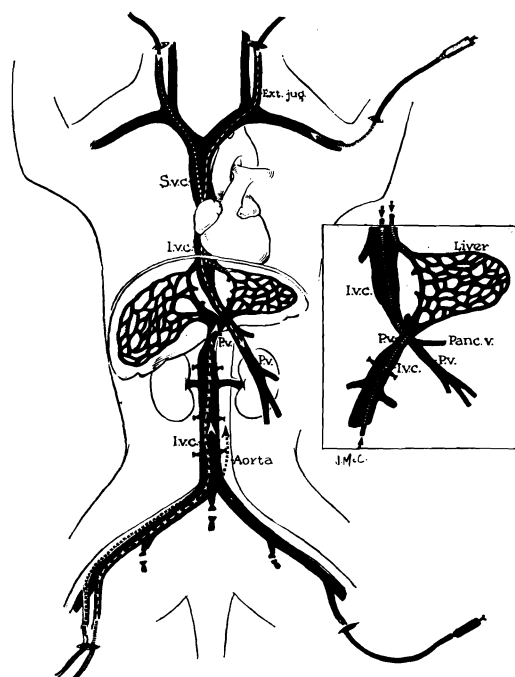


Fig. 1. Schematic representation of multiple catheter technique in dogs with transpositions. Note that all cut-downs are in the extremities or neck. Insert shows relation of catheter tips to liver.

the method of preservation depend on the requirements of the substance being analyzed. There should, however, be at least 1 c.c. of extra plasma from both the portal and hepatic vein samples for BSP determination. In this way, hepatic blood flow can be measured at the same moment as all other determinations (Fig. 4).

Administration of test drugs. Drugs can be administered systemically (via an arm vein) or with primary passage through the liver (via the inferior vena cava). Drugs given by the latter route pass through the liver with no demonstrable systemic leak (Fig. 3).

The action of drugs by the two routes can be compared on the same or alternate days with a simple rapid injection or constant infusion.

Tolerance to catheters. The animals initially tolerate multiple catheters well. With suitable body jacket, they can be allowed freedom of motion with no fluoroscopically detectable change in catheter position.

After 2 to 4 days, the dogs often stop eating and become febrile. If the catheters are removed, this deterioration is quickly reversed.

Within 2 to 4 days, the catheters have not caused thrombosis. At autopsy, liver

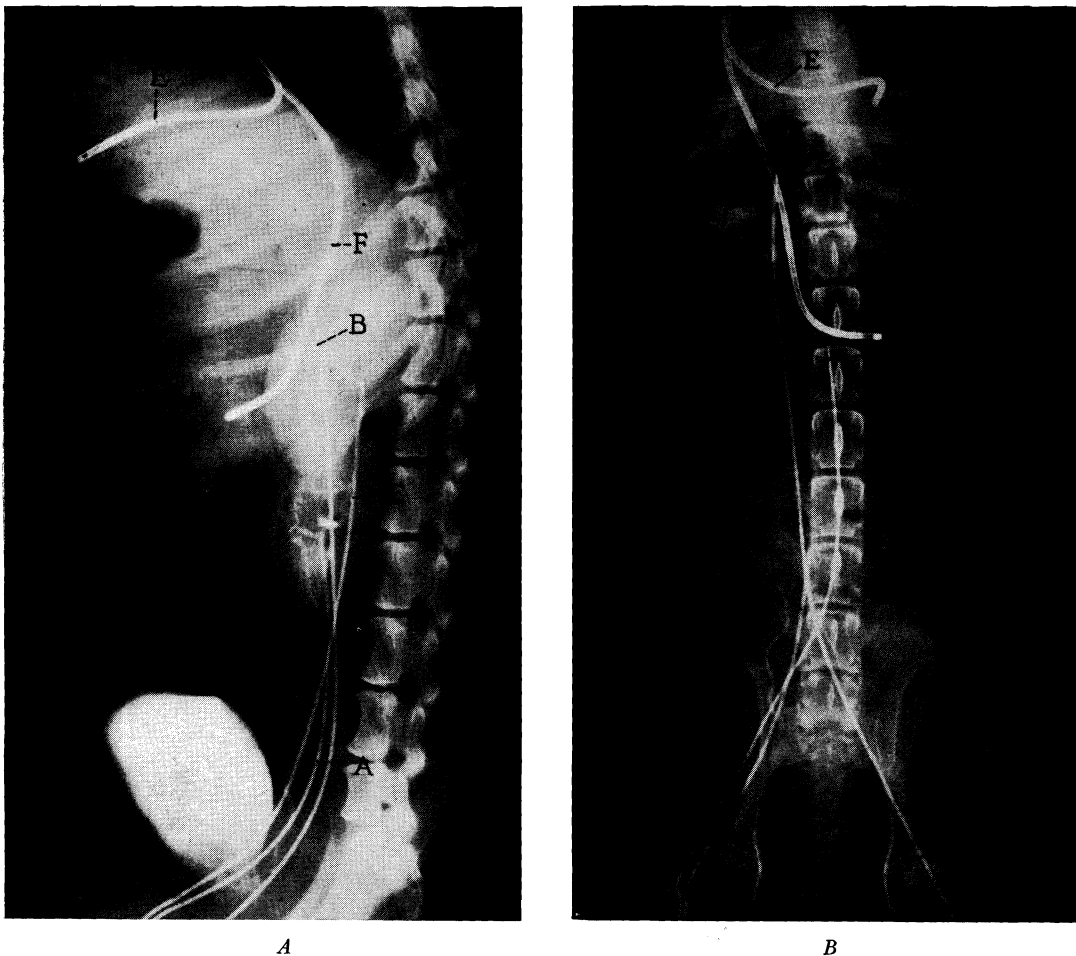


Fig. 2. Radiographic appearance of properly placed catheters. *A*, Lateral view; *B*, anteroposterior view. (*A*) Injection catheter in lower vena cava, (*B*) proximal portal vein catheter in liver hilum, (*C*) aortic catheter, (*D*) ureter, (*E*) catheter in left main hepatic vein, (*F*) splanchic catheter in distal portal vein.

bruises were commonly found in the drainage distribution of the left main hepatic vein. These were small and generally appeared to be inconsequential.

DISCUSSION

Difficulties in studying metabolism of the liver are related to the peculiarities of its double blood supply. In order to sample the portal blood in a normal dog, preliminary operation is necessary with insertion of an indwelling catheter.^{7, 9} This imposes operative stress a short time before studies are done. Clotting or dislodgment of the catheter and the clinical deterioration which occurs with long-term placement of the catheters also detract from the value of this type of preparation.

The double vascular inflow is troublesome in another way. There is no generally applicable method for determining the relative contribution of the arterial and portal systems to total hepatic blood flow. Because the nonhepatic splanchnic area is metabolically highly responsive, shifts in flow contribution from the two sources in response to drugs or stimuli could lead to serious misinterpretation of data if flow fractionation is assumed to be stable.

One approach which avoids these disadvantages is to limit the hepatic inflow to the arterial supply with the use of an Eck fistula. This technique has been used by Madison and his group⁵ in their studies of insulin effect on the liver. The primary criticism of this approach is that the liver is functionally abnormal with respect to flow, glycogen storage, dye clearance, protein synthesis, and other parameters.^{3-5, 10, 15} The animals become sickly and even response to insulin deteriorates.¹¹

These difficulties are largely eliminated by the use of the previously mentioned technique. Although the vascular supply is altered, the animals are healthy and remain so. Liver regenerative capacity, blood flow, and function are normal.^{2, 10, 13} After full recovery from the transposition, catheters can be placed through peripheral cut-downs without anesthesia or major trauma. Studies

can be initiated immediately after placement of the catheters. The nonhepatic splanchnic flow is removed from influence on the liver and replaced by systemic venous blood, the metabolic constituency of which, in many instances, is more closely parallel to that of arterial blood (Fig. 4). Thus changes in fractional flow contribution from the two sources of supply would introduce smaller errors in computing the uptake or output of hepatic metabolites.

An additional advantage lies in the ease with which gradients can be obtained across other than hepatic capillary beds. The aortic blood analysis, having just left the cardiac mixing chamber, is representative of the

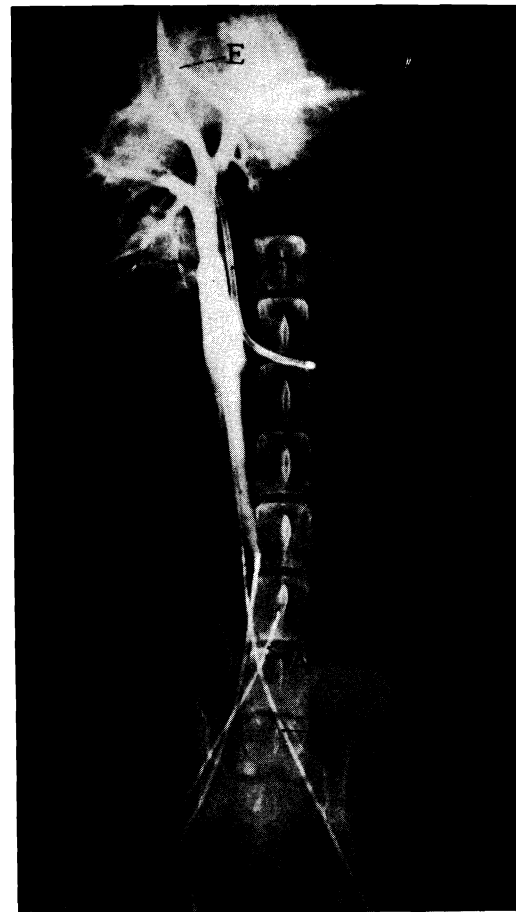


Fig. 3. Infusion of Hypaque solution through the drug injection catheter in the vena cava (C). Note that the entire dose passes through the anastomosis (G) and the liver.

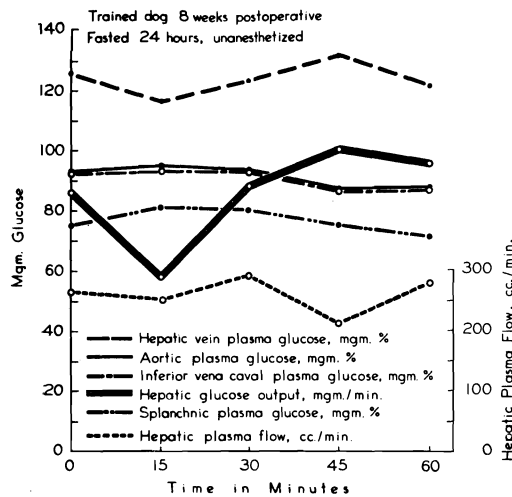


Fig. 4. Simultaneous measures obtained when glucose is the metabolite under study. Note the parallelism of the glucose in the vena caval and arterial blood.

arterial inflow of all tissues. Venous samples from the distal portal vein and the vena cava can be analyzed and the gradients determined across the gut and the hindquarters plus kidneys, respectively.

Finally, the preparation offers the means to compare the effect of drugs on any or all of the parameters mentioned above when injected systemically (in the forelegs) or directly into the hepatic vascular supply.

One technical detail that requires special emphasis is placement of the hepatic vein catheter. The anatomic studies of Shoemaker⁹ indicate that the left common hepatic vein is the best and most accessible structure for catheterization. This vein drains 40 per cent of the liver. It can be deeply penetrated, and the possibility of vena caval contamination of samples, contraverted. In our studies, catheterization of this vein was considered a prerequisite for a good experiment.

SUMMARY

A technique is described for in vivo hepatic metabolic studies, employing a multiple catheterization technique in dogs with chronic portacaval transposition. The animals are studied in the unanesthetized state

immediately after the insertion of catheters through peripheral cut-downs.

The gradient of metabolites entering and leaving the liver can be measured concomitantly with hepatic plasma flow. Additional simultaneous gradients can be obtained across the splanchnic capillary bed, or the hindquarters. Drugs can be introduced into the circulation by a systemic route or by primary injection into the hepatic circulation.

The advantages of this approach compared to other methods of evaluating moment to moment hepatic function are discussed.

The assistance of Mr. Kenneth M. Lawton was of utmost importance in the development of this technique, particularly in the training and care of the animals.

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Studies on hepatic blood flow and the rate of Bromsulphalein clearance in dogs with portacaval transposition

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Portacaval transposition, first described by Child and his group,³ has been widely used in recent years for the study of hepatic and gastrointestinal physiology. Except for a slowed rate of ammonia detoxification in the preparation, liver function is thought to be normal.^{4, 6, 9, 14}

Inasmuch as portacaval transposition involves a radical change in the vascular supply to the liver, knowledge of hepatic blood flow after operation would appear to be important. In the present study, hepatic blood flows were studied with the Bromsulphalein (BSP) method in a group of dogs with portacaval transposition, under resting unanesthetized conditions and under certain conditions of stress. Quantitative corollary data were obtained on the capacity for BSP clearance.

A modification of Child's transposition was

used in this study in order to eliminate flow variations resulting from the development of venous collaterals. All ileocaval tributaries from the inguinal ligament to the diaphragm were ligated in conjunction with transposition, and only the renal veins⁸ were spared.

METHODS

Fifteen adult mongrel dogs weighing from 12 to 20 kilograms were used. Transposition was performed under hypothermia^{15, 16} 2 months or more before testing. All tributary vessels to the iliac veins and inferior vena cava were ligated except the renal veins.¹⁶ Postoperatively, the animals were taught to lie quietly on an animal table.

On the day of testing, catheters were inserted into the left main hepatic vein and inferior vena cava¹⁶ under local anesthesia. The dogs were given a priming dose of 3 to 6 mg. BSP and then BSP was constantly infused at the rate of .05 mg. per kilogram per minute into a foreleg vein. Preliminary analyses were made of the BSP level in the vena cava. When the plasma level rose or fell appreciably, the BSP con-

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centration in the infusion was corrected by dilution or concentration to provide a constant plasma level. Subsequent variations in plasma level were mathematically corrected, with estimated plasma volume, to give the true rate of BSP clearance.²

After a resting and equilibrated state had been achieved, simultaneous samples were drawn from the hepatic vein and vena cava. These were analyzed on a Beckman DU spectrophotometer, using the hemolysis correction described by Shoemaker.¹³ Plasma flows were calculated with the Fick equation,² and blood flows computed from the hematocrit level.

RESULTS

Rate of BSP removed. The mean rate of BSP removed in 14 dogs was $.048 \pm .001$ (S. E.) mg. per kilogram per minute. Except for one animal, the spread in values was small (Fig. 1). In 4 dogs the BSP removal

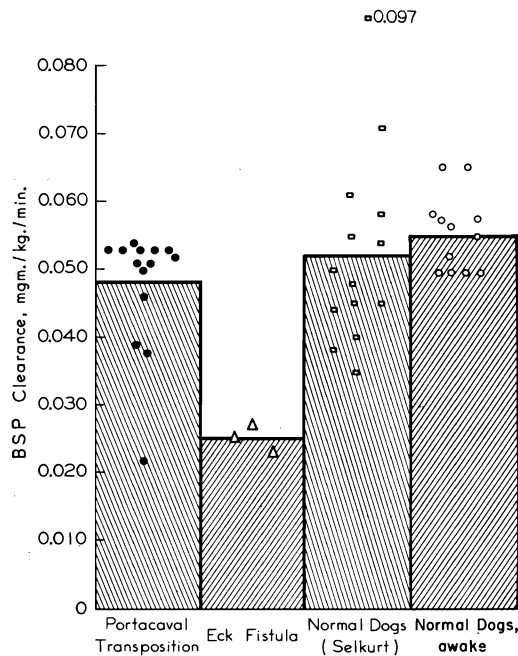


Fig. 1. BSP extraction in dogs with portacaval transposition compared to that of normal animals and those with Eck fistulas. Figures on normal anesthetized dogs calculated from Selkurt's data,¹² and normal awake animals are included for comparison.

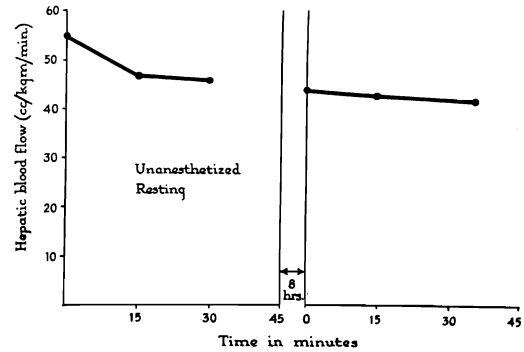


Fig. 2. Hepatic plasma flows at 8-hour interval. Note constancy of flow.

was repeated 4 months later and was found to be unchanged from the initial determination.

For comparison, BSP removal was measured in 3 dogs with Eck fistulas 2 to 4 weeks after operation. Mean rate of removal was .025 mg. per kilogram per minute (Fig. 1). The probability that the differences between transposition and Eck fistula were due to chance is less than 1 per cent.

A series of 15 unanesthetized normal dogs which had hepatic vessels that had been previously catheterized removed BSP at the rate of $.056 \pm .001$ (S. E.) mg. per kilogram per minute (Fig. 1).

Hepatic blood flow with transposition. Fourteen resting dogs were studied. All appeared to be healthy. The hematocrit level was above 30 per cent in 13 animals and above 35 per cent in 10. At least 3 flows at 15 minute intervals were obtained. In some cases, flows were obtained and repeated 8 hours later. Little variation was observed within this time limit (Fig. 2).

The mean hepatic blood flow was 43 ± 4 (S. E.) ml. per kilogram per minute. We did not observe the variations in hepatic blood flow to be related to differences in hematocrit or other obvious factors.

Effect of stress on hepatic blood flow. Muscular activity or excitement caused large and erratic rises in hepatic flow. When a source of irritation was protracted, rises in flow were sustained for long periods (Fig. 3).

The chronic placement of the catheters

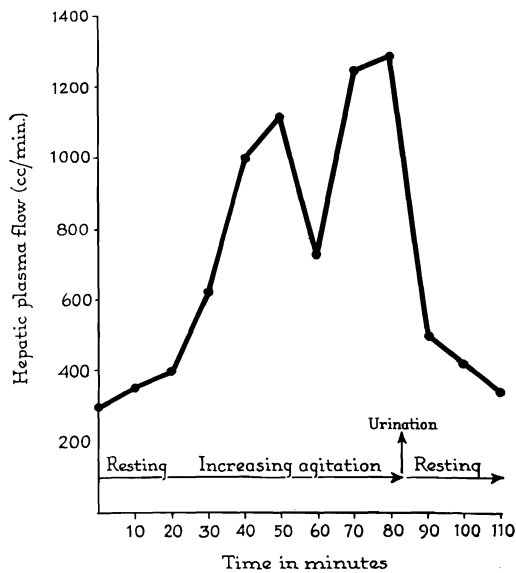


Fig. 3. Influence of painfully distended bladder on hepatic plasma flow.

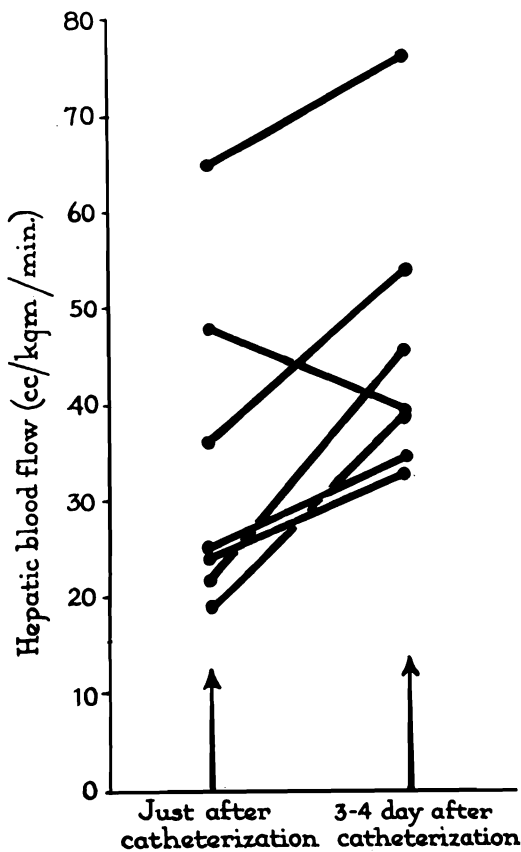


Fig. 4. Influence of indwelling catheters on hepatic blood flow. Dogs developed fever with prolonged catheterization.

was responsible for rises in flow. In 7 dogs, the catheters were left in place for 3 to 4 days. During this period, the dogs developed fever, and, in some cases, ceased eating. Hepatic blood flow rose in 6 of the 7 animals (Fig. 4).

DISCUSSION

Quantitation of hepatic blood flow after portacaval transposition has received little attention. Heer, Sylvius, and Harper,⁶ using the colloidal gold technique, reported a mean hepatic blood flow of 43.6 c.c. per kilogram per minute in 6 dogs with transposition under unstated conditions. Mean flow in the present study, using a different method, was 43 ml. per kilogram per minute in the resting unanesthetized state.

Portacaval transposition has been used in two general types of investigation: where it is desirable to avoid a direct hepatic influence on splanchnic hemodynamics or chemical constituents, and where it is desirable to divert splanchnic substances which could affect the function of the liver. The advantage of the preparation has been assumed to be that hepatic function and vascularity are normal, although vascularization is altered.^{6, 14}

Data in the present study support this concept. The mean hepatic blood flow of 43 ml. per kilogram per minute is essentially the same or slightly higher than the flows in normal dogs which have been obtained by numerous investigators with various techniques.^{1, 5, 7, 10-13, 17}

Evaluation of BSP extraction also provides a highly quantitative minute to minute evaluation of one facet of liver function. The dye clearance of .048 mg. per kilogram per minute is almost the same as that described for normal anesthetized dogs by Selkurt¹² of .052 mg. per kilogram per minute (Fig. 1) and is identical if a single anomalously low value is excluded from computation of present statistics. The BSP extraction rate of the transposed group was also similar to the rate of BSP extraction of the unanesthetized intact dogs which were studied in our own laboratories.

SUMMARY

Hepatic plasma and blood flows were determined in dogs with modified portacaval transposition. Mean hepatic blood flow was 43 ml. per kilogram per minute, approximately that expected in a normal dog. Similarly, the rate of Bromsulphalein clearance was in the range expected for normal dogs.

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