SURVIVAL OF DOGS AFTER PARTIAL OR TOTAL DEVASCULARIZATION OF THE LIVER*

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Previous experiments had shown that excision of the entire hepatic artery, from the celiac axis up to the hilum of the liver, is well tolerated if antibiotics are given. While this confirmed the results of Markowitz, *et al.*,[2] further work showed that, even without antibiotics, this procedure was not fatal in a substantial percentage of experiments. It seemed that arterial blood entering the liver through the hepatic branches of the phrenic arteries was responsible for the survivals.[2] If, in addition to the excision of the hepatic artery, the hepatic branches of the phrenic arteries were ligated, the dogs did not survive, even with antibiotics.[3] Yet, it was remarkable how small an arterial blood supply was sufficient to prevent liver necrosis. This seems to have its explanation in the ability of the liver to take enough oxygen from the portal blood. However, since interruption of the entire arterial blood supply of the liver by complete excision of the hepatic artery and ligation of the hepatic branches of the phrenic arteries was fatal regularly, the conclusion seemed justified that the oxygen provided by the portal blood alone is insufficient to prevent liver death. Furthermore, since performance in one stage of an Eck-fistula and excision of the hepatic artery is also regularly fatal,[5] the hepatic branches of the phrenic arteries alone are obviously insufficient to prevent fatal liver necrosis. The liver apparently needs more oxygen than the portal blood alone or the hepatic branches of the phrenic arteries alone can supply, if the rest of its blood supply has been cut off in one stage.

Recently, we found that ligation of two-thirds of the branches of the portal vein did not damage the liver materially. However, combining such ligations with complete excision of the hepatic artery caused necrosis of that portion of the liver which had been deprived of both hepatic arterial and portal venous blood. The rest of the liver which was without hepatic arterial circulation but which received portal blood, did not show appreciable changes if antibiotics were given postoperatively.[4]

The following is a report on a new series of experiments in which we have tried to gain additional knowledge on survival of animals following interference with the hepatic arterial and venous blood supply, by modifying the operative procedures and by performing them in several stages.

METHOD

Thirty-five male and female mongrel dogs of 8 to 15 Kg. weight were operated upon aseptically under pentothal sodium anesthesia. Overdosage of the anesthetic was avoided, since interference with liver circulation decreased tolerance for the barbiturate. Penicillin and streptomycin were administered before or immediately after the operation, and for the first three postoperative days; 300 ml. of 5 per cent glu-

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cose solution was given intravenously after operation or for a longer period of time, if necessary. Autopsies were performed on all dogs and a non-diffusable dye[3] was injected into the aorta or the portal vein, or both, to ascertain the extent of interference with the vascular supply of the liver.

Group A. In 11 dogs, approximately three-fourths of the portal branches were ligated in the hilum of the liver as described in our previous paper,[4] a cholecystectomy was performed, and the common hepatic artery was ligated and cut between its origin from the celiac axis and the origin of the gastroduodenal artery. Bleeding from the stump of the hepatic artery leading to the liver was encountered regularly, so that we felt justified in assuming that the liver would get some arterial blood by reverse flow through the gastroduodenal and the right gastric arteries. In two of these dogs the hepatic branches of the phrenic arteries were ligated also.

Group B. In nine dogs, branches of the portal vein were ligated and a cholecystectomy performed as in the previous group, but the hepatic artery was excised completely from the celiac axis to the hilum of the liver.

Group C. In six dogs the above procedure was done in two stages. Ligation of branches of the portal vein was followed in three dogs two days later, and in three dogs seven days later, by complete excision of the hepatic artery and cholecystectomy.

Group D. In nine dogs the main stem of the portal vein was constricted with umbilical tape, which was tied over the tip of a curved hemostat. This procedure, though gradually leading to complete closure of the vein, assured some flow of portal blood for a period of time. The afferent portion of the portal vein was somewhat distended following this procedure, but the bowel did not show signs of congestion. In four of these dogs, the hepatic artery was excised and cholecystectomy was performed at the same operation, and in two dogs four days and in three dogs seven days later. The separation of these procedures into two stages enabled us to apply a greater degree of constriction to the portal vein than at the one-stage operation. When marked portal constriction and excision of the hepatic artery were performed at the same time, a number of dogs died shortly after the operation, and we were uncertain whether they had died from too much portal constriction or from the combined procedure. Only with the two-stage procedure were we able to evaluate the combination of more extensive constriction of the portal vein with excision of the hepatic arterial supply.

Cholecystectomy was performed in all experiments in which the arterial blood supply to the liver was interrupted, since previous experience had shown that interference with the arterial blood supply, though not damaging the liver noticeably, may lead to necrosis of the gallbladder.[2]

RESULTS

Group A. Of the 11 dogs with extensive ligation of portal branches and transection of the common hepatic artery, five died within 48 hours with extensive liver necrosis. The peripheral stump of the hepatic artery contained a clot which blocked the root of the gastroduodenal artery in some of the dogs. In none of these dogs did any dye injected into the aorta enter the liver through the porta hepatis, indicating that no arterial supply to the liver had been established by reverse flow through the gastroduodenal and right gastric arteries, as had been assumed at operation from the active bleeding of the distal stump of the severed hepatic artery. Thus, conditions in these dogs were identical to those in *Group B*, where the hepatic artery had been excised completely. The other six animals, including the two in which the hepatic branches of the phrenic arteries had been ligated at the same time, survived the op-

eration, but one of them developed jaundice one week postoperatively and died two weeks later. Autopsy revealed an abdominal hemorrhage, the origin of which could not be found; the liver was very small and of yellowish-green color; the bile ducts were not obstructed; the portal vein had closed completely, and no dye injected into the portal vein below the obstruction entered the liver; injection of dye through the aorta showed only tiny arterial branches entering the liver along the vena cava and from the phrenic arteries. Microscopic sections* of the liver revealed extensive central necrosis, and in one portion additional midzonal necrosis of the liver.

Another dog died three weeks postoperatively, without significant findings at autopsy. One-third of the portal branches were patent and, following injection through the aorta, the liver became filled with dye through the gastroduodenal artery; grossly, the liver appeared completely normal, and microscopically it showed central congestion, with tiny areas of central necrosis. Of the remaining four dogs, one was sacrificed two weeks after the operation. Autopsy showed a normal liver which had received arterial blood through the patent gastroduodenal artery. The other three dogs are still alive and in good physical condition.

Group B. All nine dogs with extensive ligation of branches of the portal vein and complete excision of the hepatic artery in one stage died with partial liver necrosis within three days.

Group C. In six dogs, the above procedure was performed in two stages. Three animals in which partial ligation of the portal vein was followed by total excision of the hepatic artery two days later, died within 36 hours with liver necrosis. Microscopically, the liver showed extensive necrosis where hepatic arterial and portal circulation had been blocked, and nothing but congestion where only the arterial circulation had been eliminated. The three dogs in which the second stage was done after seven days survived. However, one died 17 days after the second operation, with diffuse peritonitis originating from complete colliquation necrosis of the left lobe of the liver; the rest of the liver was soft and had lost its normal pattern. Injection of dye into the aorta showed that some arterial blood had entered the liver through rather small hepatic branches of the phrenic arteries, and through a network of filamentous arteries which had developed around the portal vein, a frequent finding following excision of the hepatic artery. Therefore, the total amount of arterial blood available to the liver must have been exceedingly small. Injection of dye into the portal vein showed that only about one-third of it had been left open. The other two dogs were reoperated upon seven weeks after the second-stage operation. In one dog we found a normal-appearing liver with an apparently unobstructed portal vein. Upon taking a biopsy from the liver, appreciable venous bleeding from the cut surface was encountered. It seemed as if the ligature of the portal branches had disappeared. The other dog had considerable adhesions around the liver, which was rather dark in color. The portal vein appeared congested. A biopsy was taken from the left liver lobe, the portal branches of which had been ligated at the first operation, and no bleeding at all occurred from the cut surface. Microscopic examination of the biopsy revealed enlarged portal fields with proliferated cholangioles, and extensive degenerative changes suggesting necrobiosis. At the end of the exploration, the hepatic branches of the phrenic arteries were ligated in both dogs. This was tolerated well, and the animals are still alive.

Group D. All four animals, in which at one operation the vena portae had been

* We are obliged to Dr. P. Szanto for reviewing the slides.

constricted and the hepatic artery excised, survived. Two of the animals were reoperated upon five and a half and eight weeks later. Multiple adhesions were found between liver, abdominal wall, and loops of bowel. The liver was not discolored in either dog, but it was more friable than usual. The constricted portal vein was ligated completely, and biopsies of the liver were taken. No bleeding from the cut surface was encountered in one dog, and very little bleeding in the other. The other two dogs were reoperated upon six and eight weeks, respectively, after the first operation. A small, necrotic lobe of liver adjacent to the previously excised gallbladder was found in one dog, but no other findings, except for multiple adhesions of the normal-looking liver to neighboring structures. The portal vein was ligated completely, the hepatic branches of the phrenic arteries were ligated, and liver biopsies were taken, with practically no bleeding from the liver. Microscopic examination of the biopsies showed some focal necrosis in one dog, and no significant changes in the others.

These four dogs are still alive several months after the preliminary constriction of the portal vein combined with excision of the hepatic artery, and subsequent complete ligation of the portal vein, with ligation of the hepatic branches of the phrenic arteries in two of them.

In the remaining five dogs more extensive constriction of the portal vein and excision of the artery had been performed in two stages. Two animals, in which the second stage had been done four days later, died within two days after the second operation. Of the three in which the second operation was performed seven days later, one died the next day, one apparently was dying after two days and was sacrificed, and the third dog died after seven days, with extensive bilateral pneumonia but with no liver damage; the portal vein was constricted, but the entire liver was filled easily with dye injected below the constriction of the portal vein. The hepatic branches of the phrenic arteries were well developed, and there were two small branches of the left gastric artery which entered the liver outside of the liver hilum and had, therefore, been overlooked. The liver of this animal was normal, while the livers of the other four animals showed extensive necrosis grossly and microscopically.

DISCUSSION

Of the dogs with extensive ligation of the portal vein and ligation and transection of the common hepatic artery, apparently those died which did not get arterial blood into the liver by reverse flow through the gastroduodenal and right gastric arteries. If such a reverse flow does not occur, the conditions are the same as if the hepatic artery had been excised completely which, in our experience, was always fatal. These experiments, moreover, show that we are not justified in assuming that arterial blood will certainly reach the liver through collaterals after ligation of the common hepatic artery, not even when we see active bleeding from the distal stump of the artery, as was the case in our dogs. The actual persistence of this collateral circulation probably depends on anatomical, as well as on hydromechanic, conditions, and on vasopastic reactions which cannot be predicted. This same fact is, in our opinion, also responsible for the experience of Rappaport,[5, 6] where performance of an Eck-fistula followed 24 to 48 hours later by ligation of the common hepatic artery, was tolerated well in some dogs, and followed by fatal or non-fatal coma in others.

If arterial blood reaches the liver by reversed flow in the gastroduodenal and right gastric arteries, it can be only a fraction of the normal hepatic arterial blood flow, until compensatory changes in the blood vessels have taken place. However, this de-

creased amount of arterial blood seems sufficient to prevent liver necrosis in the areas where the portal circulation has been interrupted, even when the additional arterial blood supply through the hepatic branches of the phrenic arteries has been interrupted at the same time.

In previous reports we have pointed out that the portal blood alone seems not sufficient for the oxygenation of the liver, and that some additional arterial blood has to be available to prevent fatal liver necrosis. The present experiments show that a fraction of the hepatic arterial blood supply seems sufficient to prevent liver necrosis in the part of the liver where the portal blood supply has been cut off completely. This seems to show that the assumption of some authors[7] that more than 50 per cent of the oxygenation of the liver is provided by the portal blood is not acceptable. Obviously, for supply of oxygen, the hepatic artery is more important than the portal vein. Otherwise, we could not explain why an animal dies of liver necrosis if the liver receives only portal blood, while no necrosis develops if the greater part of the liver is deprived of its portal blood and has only a fraction of the hepatic arterial blood left for oxygenation.

If extensive ligation of portal branches was combined with complete excision of the hepatic artery, all animals died within a few days. If excision of the hepatic artery was done two days after ligation of the portal branches, the animals died likewise. However, if the second operation took place after seven days, the dogs survived, though one of them died a few weeks later from complications of partial necrosis. This suggests that compensatory mechanisms take place, which protect the liver against the effects of a drastically reduced circulation. Apparently, it takes a certain time until these compensatory mechanisms take effect, since a two-day interval was not sufficient to prevent fatal liver necrosis, while seven days were. The prevention of bacterial growth cannot play a part in this, as all animals received the same amounts of antibiotics after each operation. Following partial ligation of the portal vein, we did not find increased collateral arterial circulation from the phrenic arteries or from other sources, which could explain these results. Moreover, we could demonstrate that the portions of the liver with ligated portal branches did not get portal blood from the intrahepatic anastomoses with other portal branches, neither immediately nor after an interval of time. Thus, the survival of the animals is evidently not due to gradually developing arterial collaterals, not to increased intrahepatic portal anastomoses, and not to the action of antibiotics. The liver of the dog appears to be able to survive a drastic reduction of its arterial and venous blood supply if this is done in stages, as has also been shown by Rappaport.[5]

The last group of experiments (D) showed that moderate constriction of the portal vein, combined with complete excision of the hepatic artery, was tolerated. Performed as a two-stage procedure, which permitted more drastic constriction of the portal vein, it caused fatal liver necrosis in most dogs. Only one out of five dogs had no liver necrosis, and it might well be that less portal constriction had been produced here than in the other four dogs.

The portal vein has a wide lumen, which possibly can be narrowed considerably before appreciable interference with its blood flow will take place. However, it is safe to assume that even moderate constriction of the portal vein, as performed in our one-stage operations, led to some decrease of portal blood supply of the liver. Yet, this decreased portal blood flow, combined with some arterial blood coming in through the hepatic branches of the phrenic arteries, was sufficient to prevent liver necrosis after total excision of the hepatic artery.

However, complete excision of the hepatic artery and more pronounced constriction of the portal vein led, as a rule, to fatal liver necrosis, though the two-stage operation might have facilitated adaptive changes of the liver to the impaired circulation.

It is peculiar that drastic constriction of the portal vein, followed seven days later by complete excision of the hepatic artery, caused fatal liver necrosis in the majority of animals, while complete occlusion of the greater part of the branches of the portal vein, followed by excision of the artery after the same interval, was tolerated rather well. In the former procedure the portal blood supply to the entire liver is diminished drastically, whereas in the latter procedure part of the liver gets its portal blood supply, possibly even increased amounts of it, while the greater portion of the liver is deprived of it completely. The reason for this difference may be in different adaptive reactions of the liver following the two kinds of interference with its portal blood supply, but our observations are too small in number to permit definite conclusions.

The four dogs of *Group D*, which had survived moderate constriction of the portal vein and excision of the hepatic artery, survived a subsequent complete ligation of the portal vein; in two animals, additional ligation of the hepatic branches of the phrenic arteries was performed. These four dogs showed no bleeding, or practically no bleeding, from the cut surface of the liver at the second operation, performed six to eight weeks after the first one. Rappaport[5] has reported that he observed no bleeding of the cut surface of the liver 48 hours after ligation of the common hepatic artery, and performance of a partial Eck-fistula. We have seen a number of dogs which did not show any bleeding from the cut surface of the liver six to eight weeks and longer after various devascularizing procedures, and which still seemed to be in good physical condition.

Of these last four dogs which were operated upon, in two the liver got some blood through the hepatic branches of the phrenic arteries, but the only possible blood supply of the livers of the other two dogs would be through arterial filaments along the vena cava or the bile ducts and through adhesions. The fact that the incised liver did not bleed at all even before the phrenic branches had been ligated, showed that no appreciable amount of blood was reaching that part of the liver. This suggests that it is not correct to assume that blood coming to the liver through newly formed blood vessels in adhesions and through secondarily developed filamentous arteries will reestablish the entire circulation of the liver.

That an organ of the size and with the manifold functions of the liver can survive on arterial blood supplied through insignificant arterial filaments which are too small to provide adequate oxygenation contradicts well established physiologic facts. It looks as if the liver, under certain conditions, is either capable of developing a metabolism which permits survival of its cells with a minimum of oxygen, or it has a source of oxygen outside of its regular blood supply which it can utilize. Either of these processes may require a gradual transition, and may be slow in taking effect. This could explain why deprivation of the liver of its entire blood supply will be tolerated only if it is done gradually, in appropriately spaced stages.

SUMMARY

The effect of interference with the arterial and the venous blood supply of the liver was studied.

Various partial or complete devascularizing procedures were performed in one or two stages.

A fraction of the normal hepatic arterial blood supply, i.e., arterial blood reaching

the liver by reverse flow in the gastroduodenal artery, is sufficient to prevent necrosis if the portal blood supply to part of the liver is interrupted at the same time. However, the establishment of such reverse flow is uncertain, and active bleeding from the peripheral stump of the hepatic artery at the time of operation is no guarantee for it.

Complete interruption of the hepatic arterial blood supply, combined with ligation of part of the branches of the portal vein, leads to liver necrosis if performed in one stage, and is rather well tolerated if performed in two stages with an interval of one week.

Moderate constriction of the portal vein, combined with excision of the hepatic artery, is tolerated well.

More extensive constriction of the portal vein and excision of the hepatic artery was usually fatal when performed as a two-stage procedure, with an interval of up to one week between the two operations.

The dog can survive complete interruption of all arterial and portal blood supply, if this is done in appropriate stages.

In a number of experiments the liver bled very little or not at all when biopsies were taken a few weeks after interruption of its blood supply. This shows that the circulation in the entire liver had not been restored by collaterals or anastomoses.

The results of some of the two-stage procedures show that the liver can adjust itself gradually to a drastically reduced arterial and venous circulation.

The liver may possess compensatory mechanisms for its oxygen needs, the nature of which are not clear, processes which do not seem to be in line with accepted physiologic concepts.

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